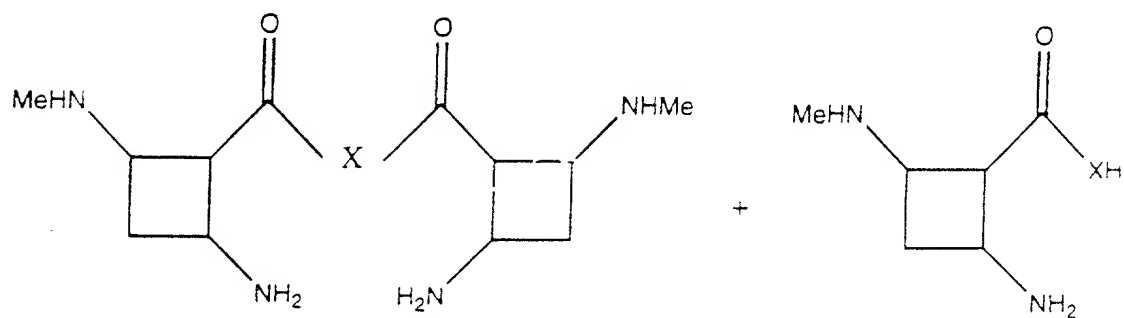
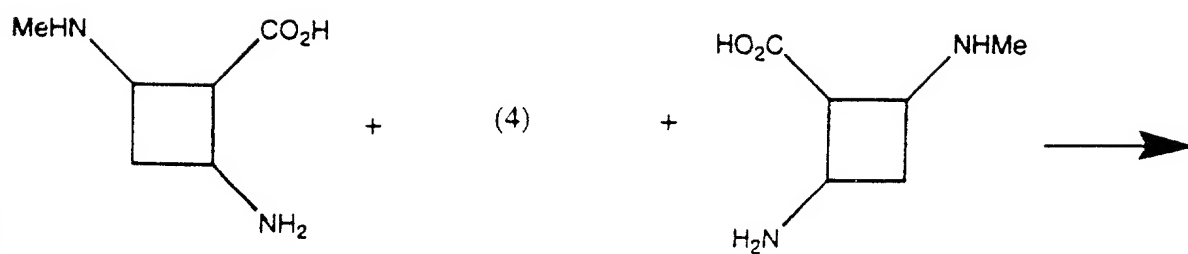


REACTION SCHEME 2

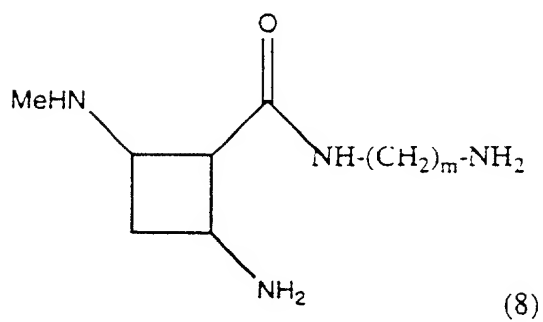
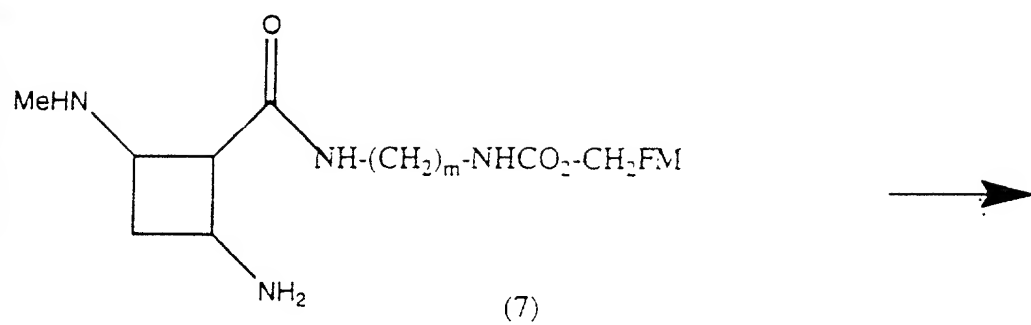
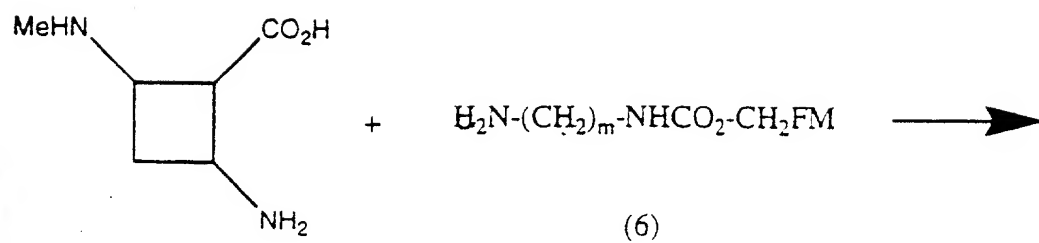


Formula 1

(5)

FIGURE 1

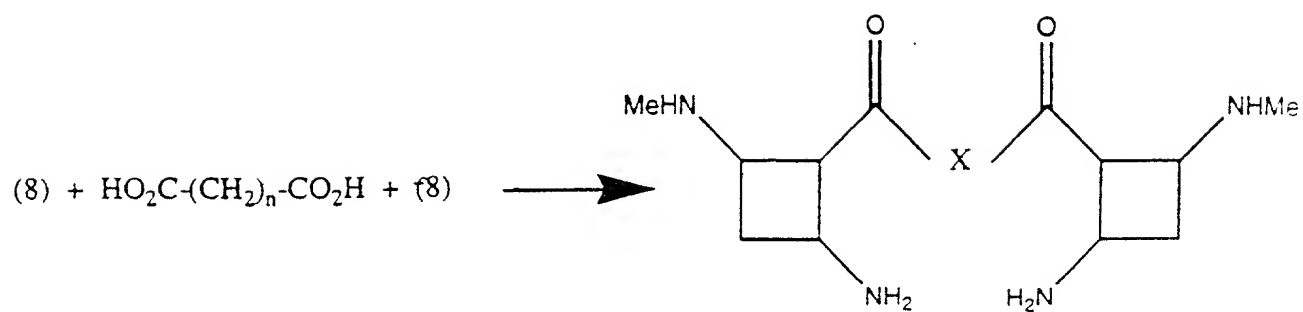
# REACTION SCHEME 3



Where FM represents 9-fluorenyl., and m is an integer of 1-20

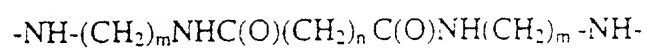
FIGURE 2

# REACTION SCHEME 4



Formula I

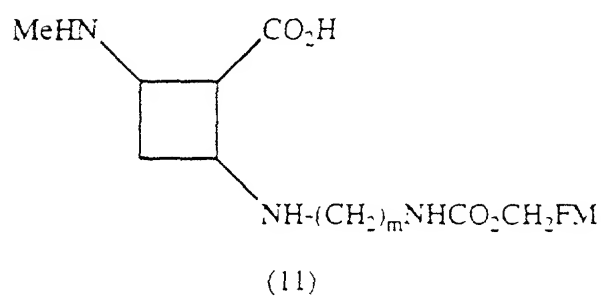
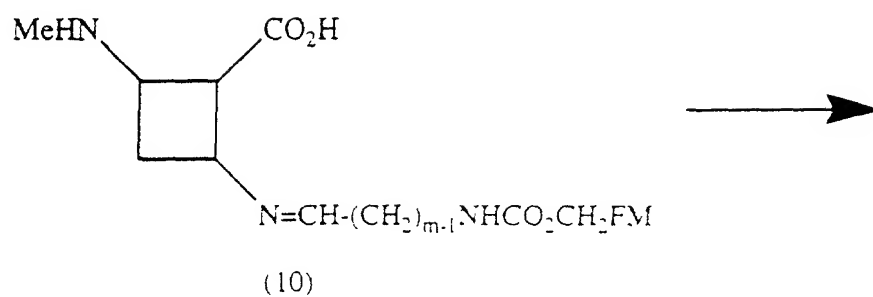
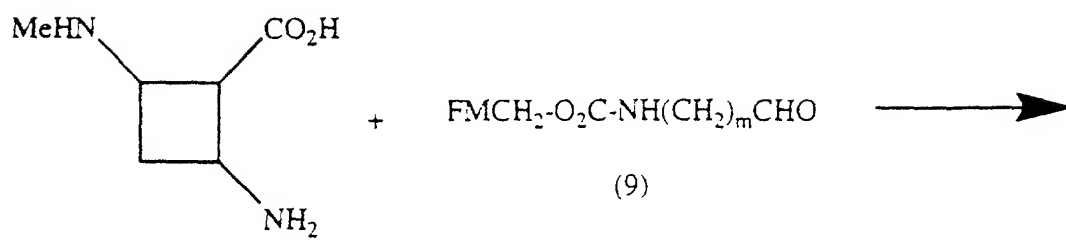
where  $X$  is a linker of formula:



in which  $m$  and  $n$  are independently integers of 1-20.

FIGURE 3

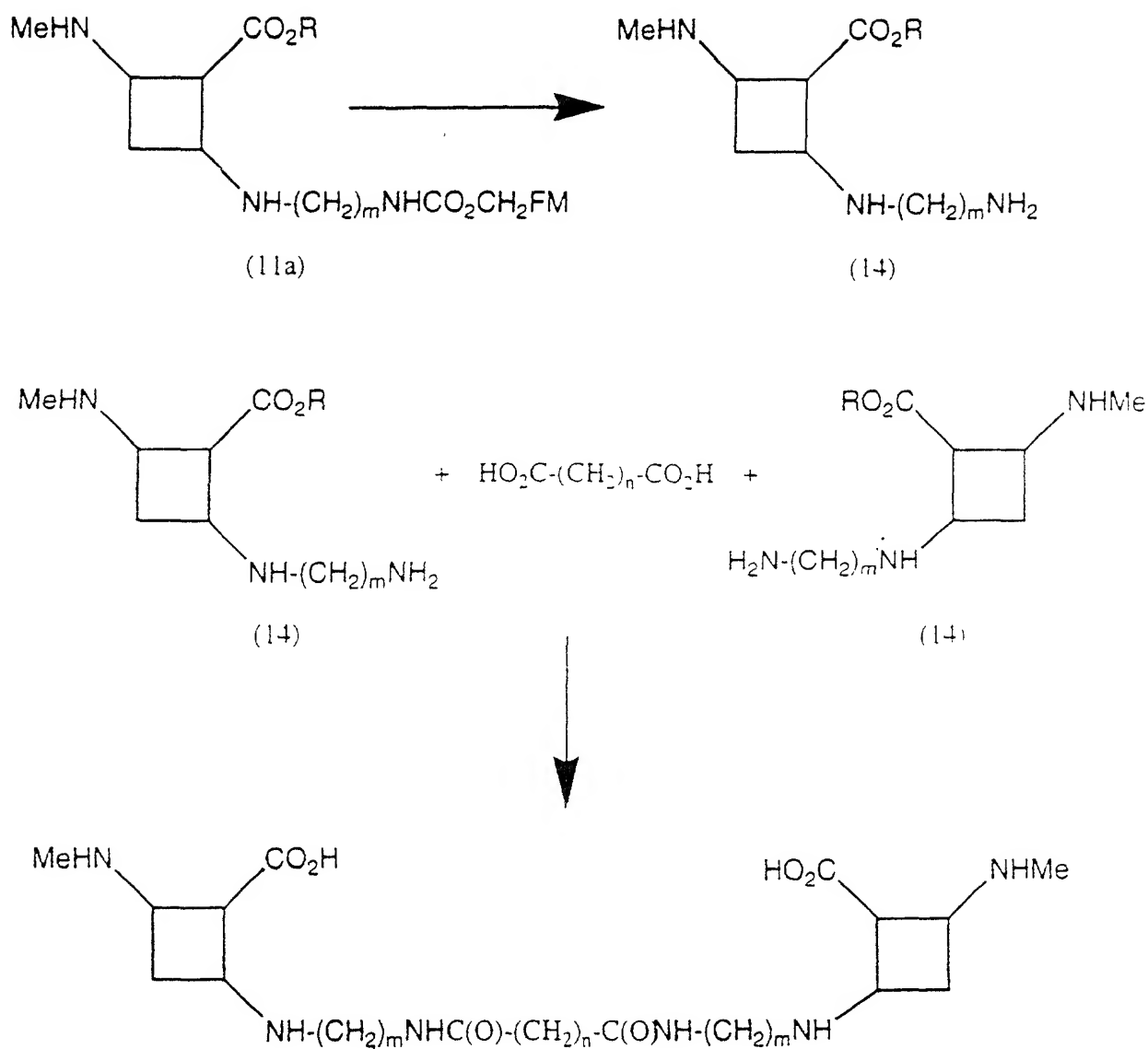
# REACTION SCHEME 5



in which  $m$  is an integer of 1-20, and FM is 9-fluorenyl.

FIGURE 4

REACTION SCHEME 6



Formula I

where R is a protecting group, such as an ester, m and n are as defined above, and FM is 9-fluorenyl

FIGURE 5

# REACTION SCHEME 7

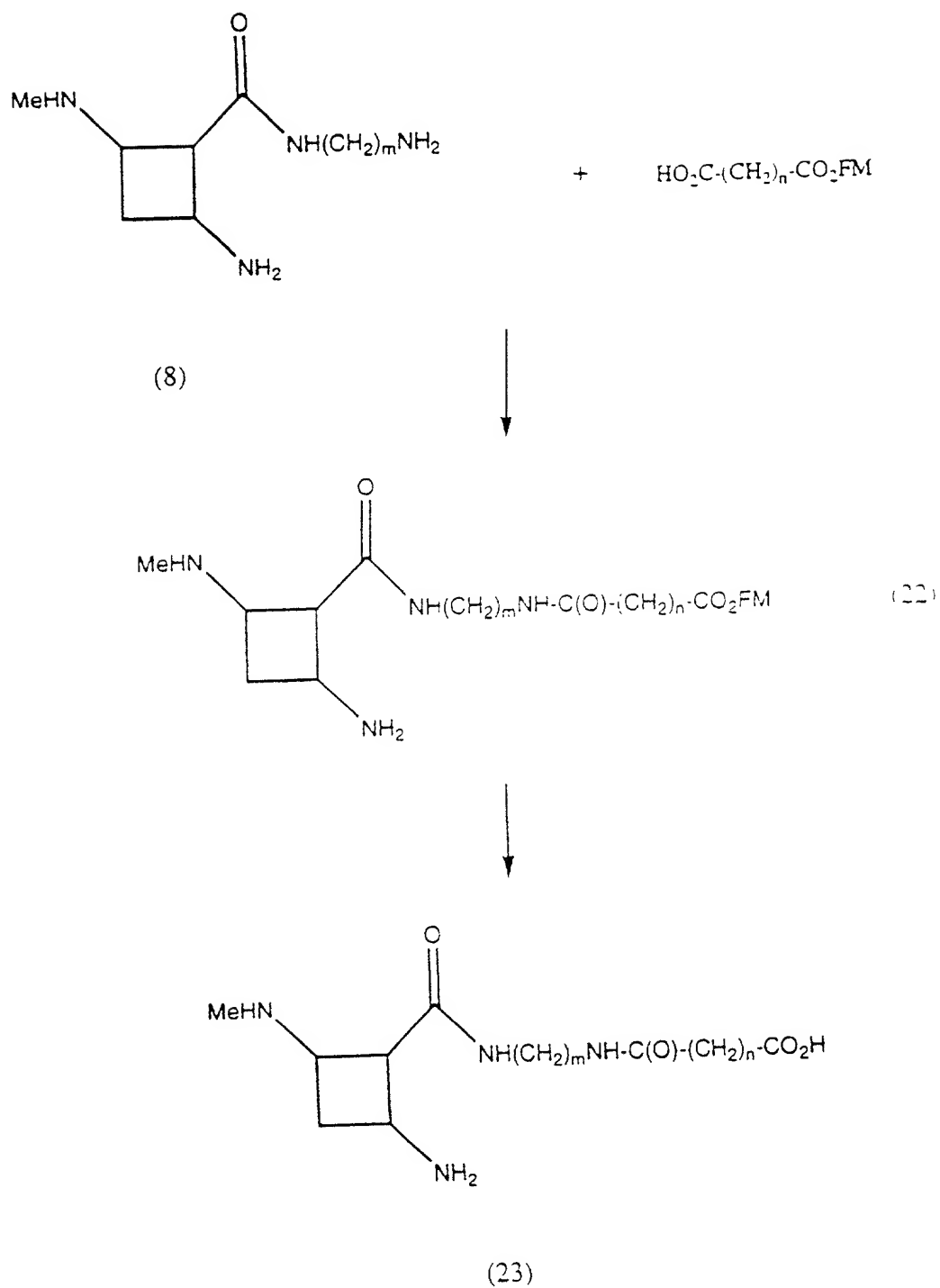
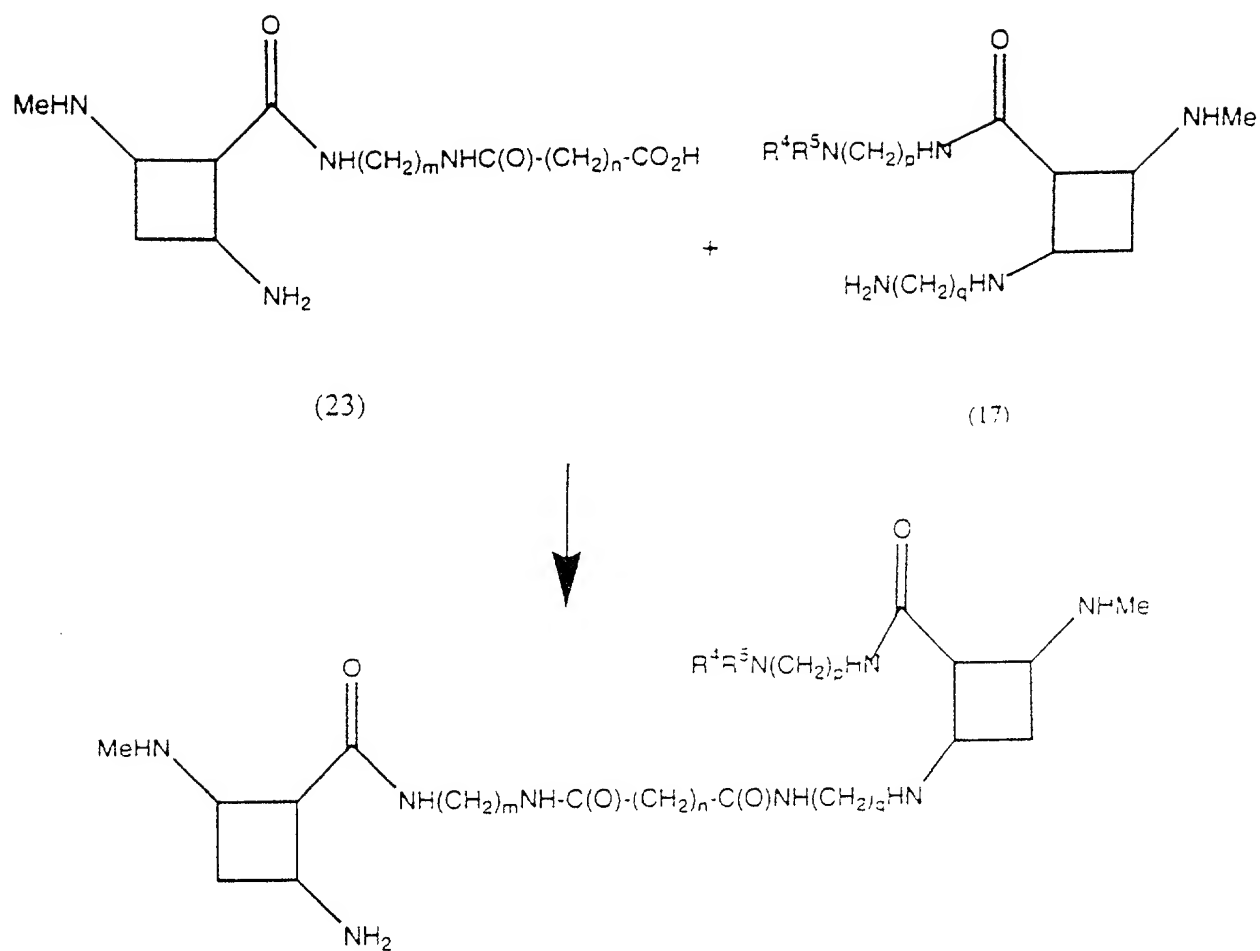


FIGURE 6

REACTION SCHEME 8



Formula I

FIGURE 7

# REACTION SCHEME 9

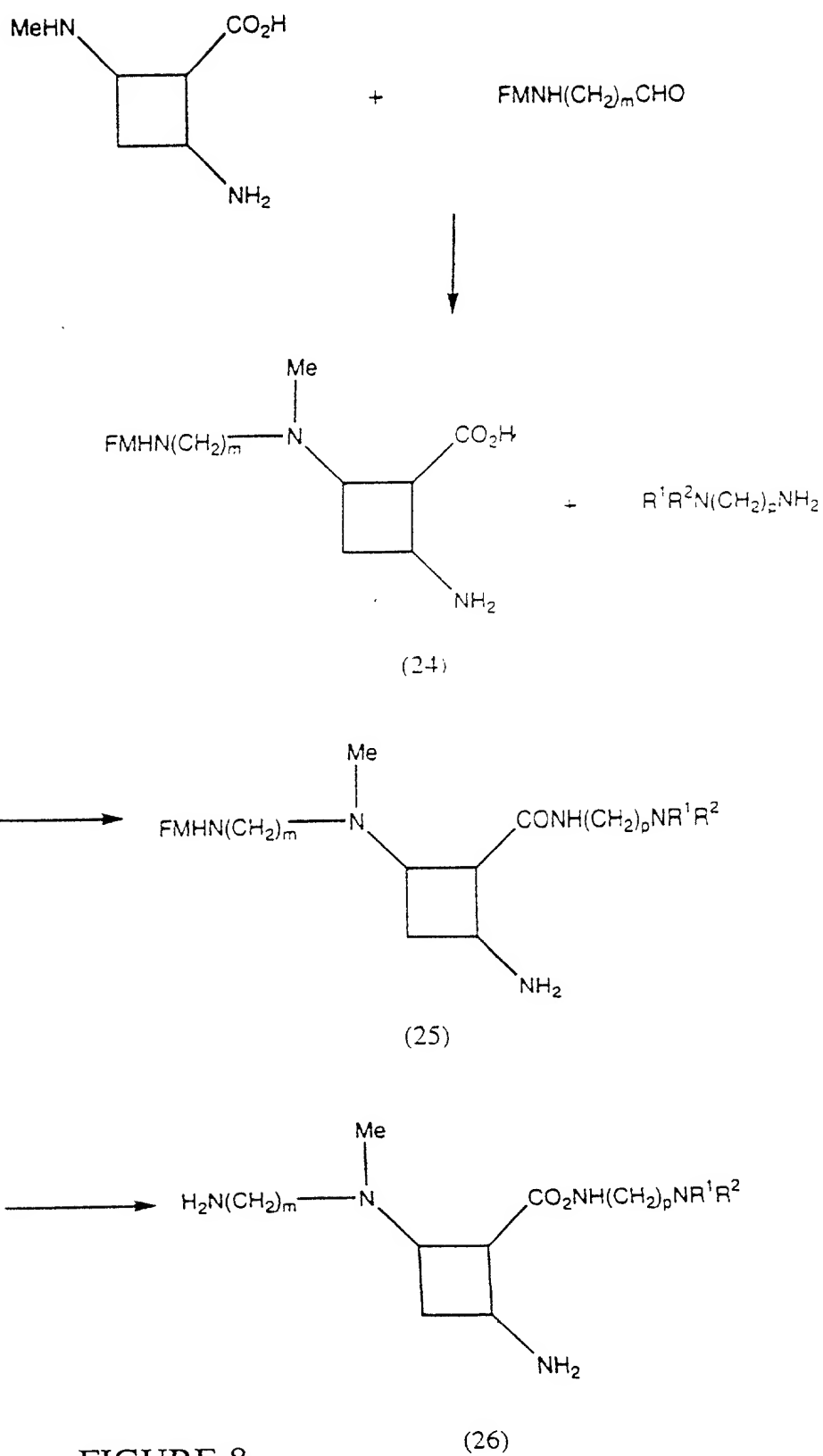
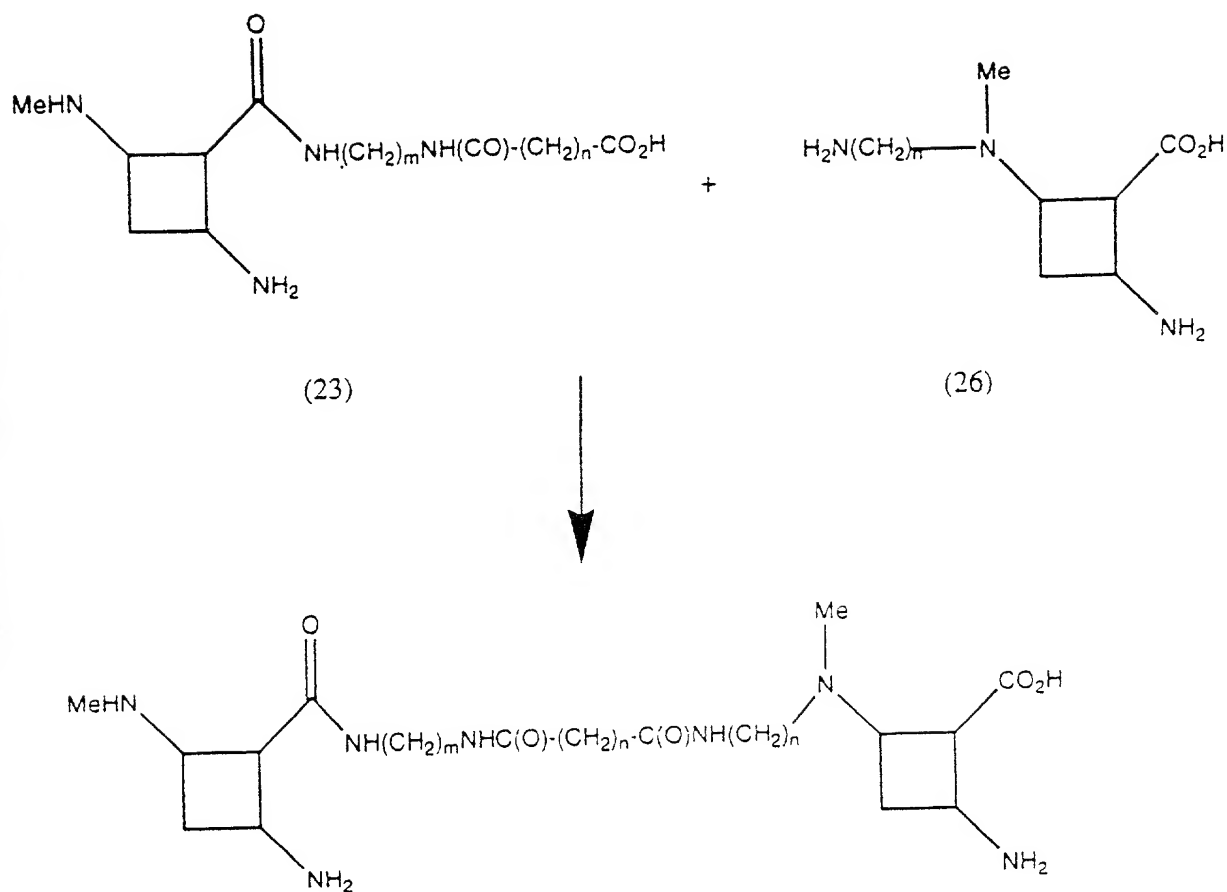


FIGURE 8



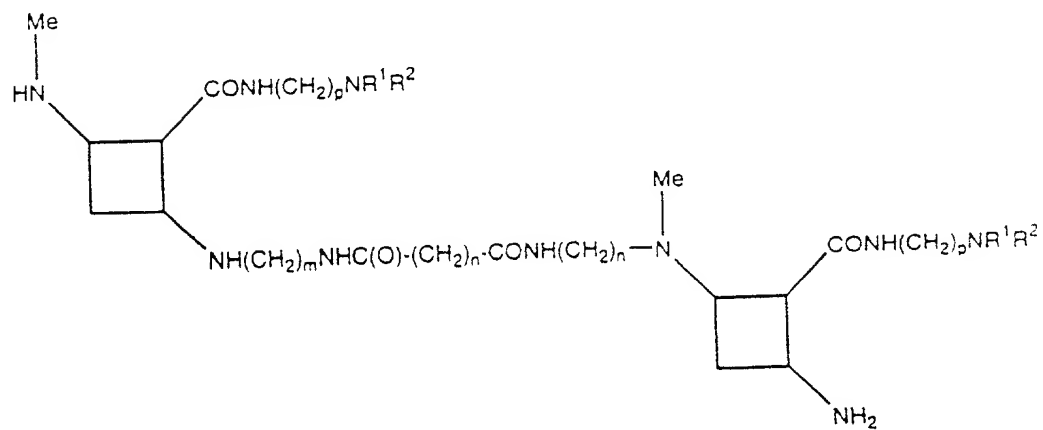
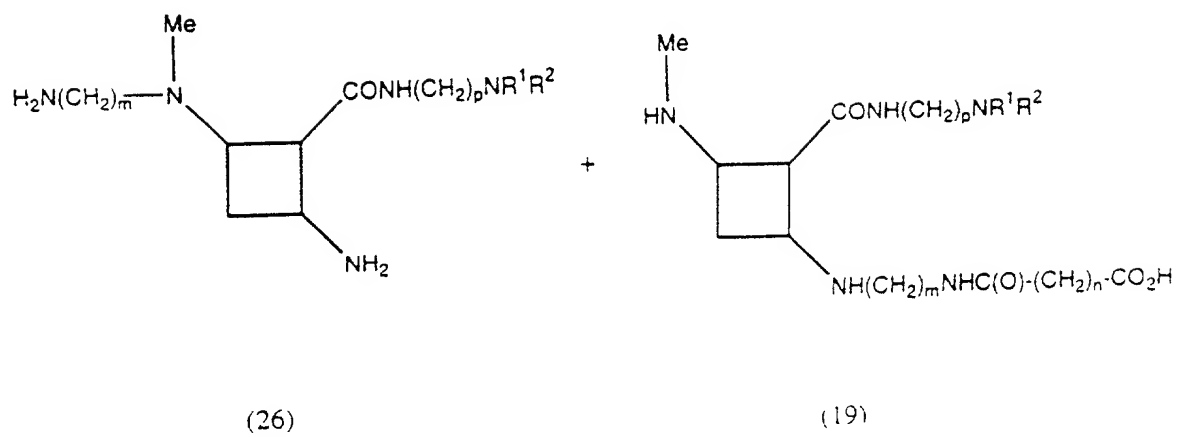
# REACTION SCHEME 10



Formula I

FIGURE 9

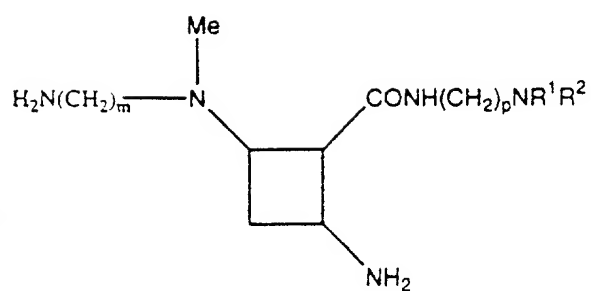
REACTION SCHEME 11



Formula I

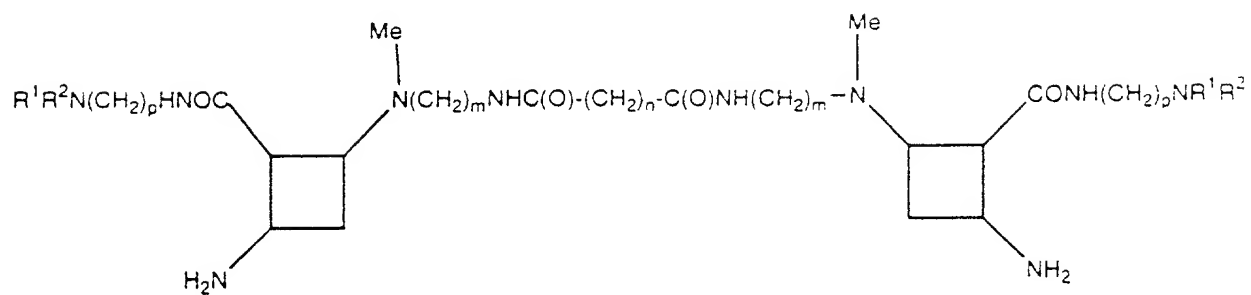
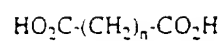
FIGURE 10

REACTION SCHEME 12



(26)

+



Formula I

FIGURE 11

*Examples of dimeric display*

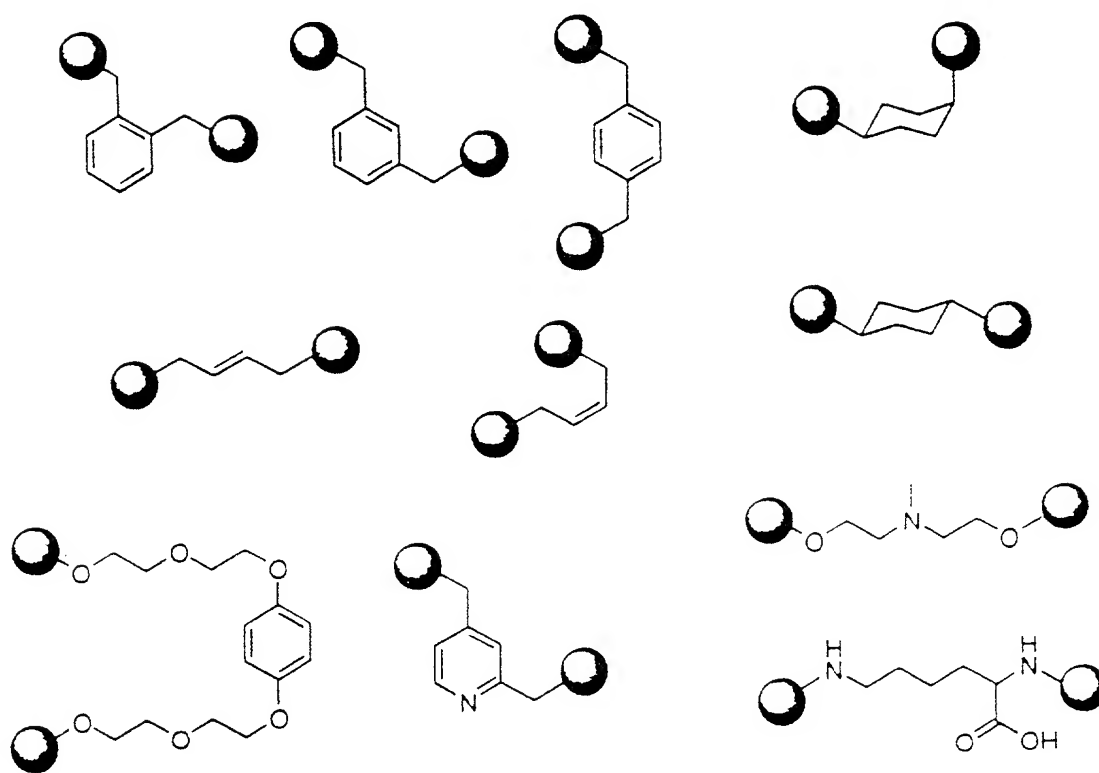


FIGURE 12

*Examples of trimeric display*

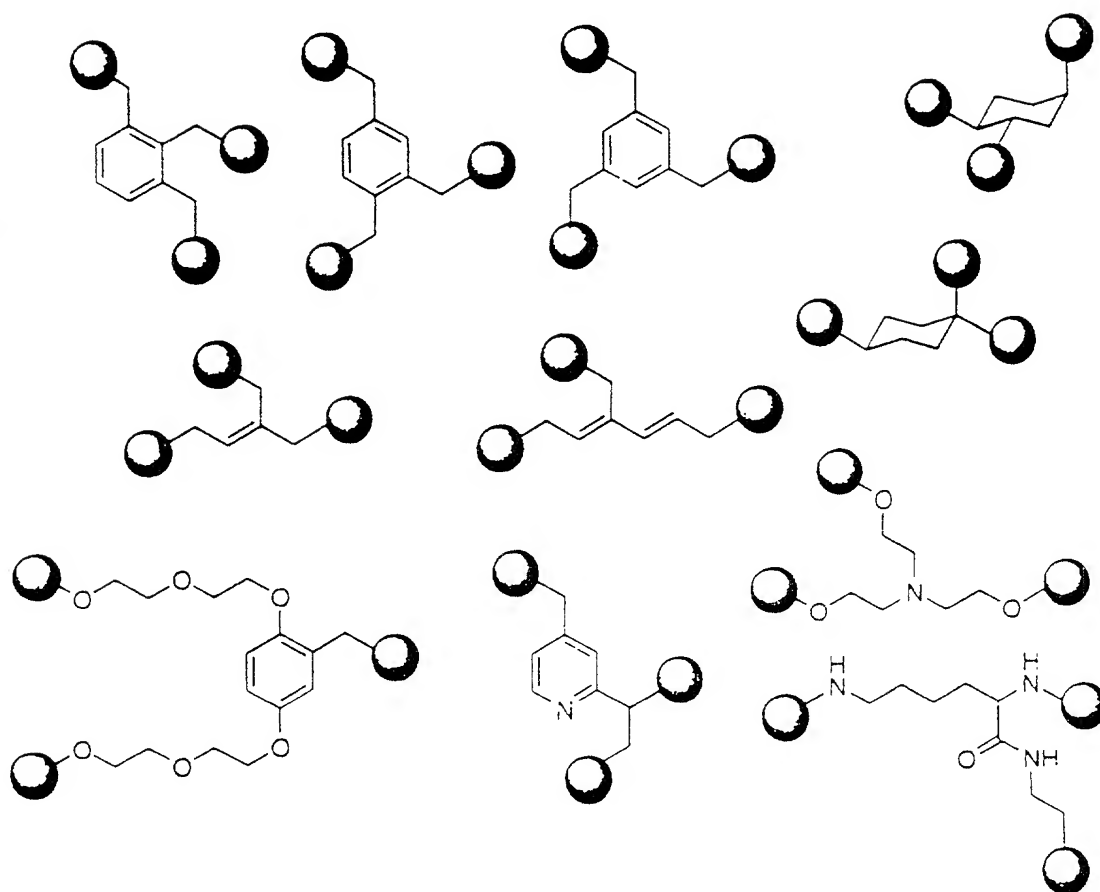


FIGURE 13

[illegible]

# Examples of higher order polyvalent display

1004564-1

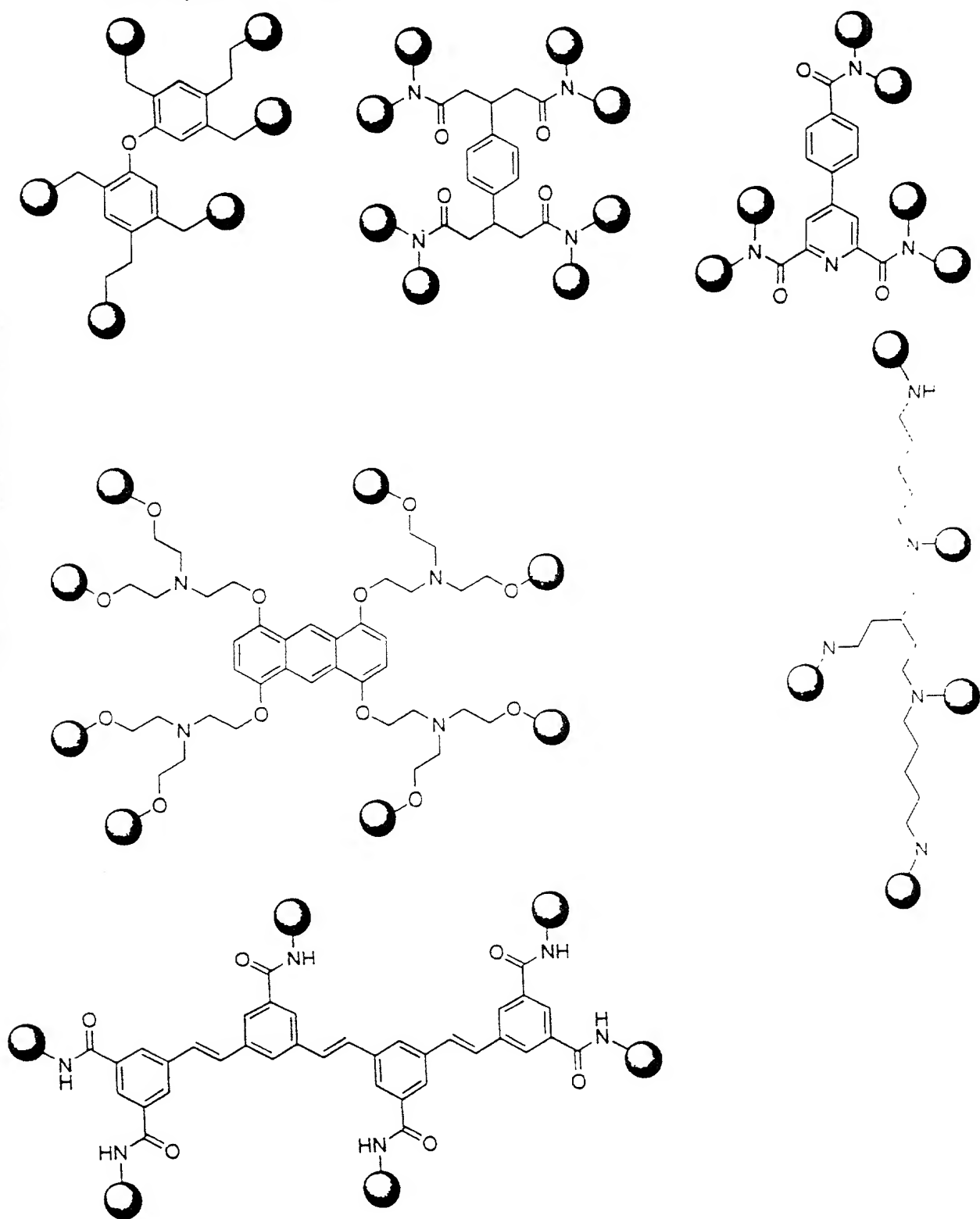
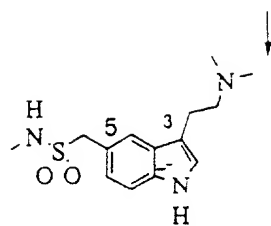
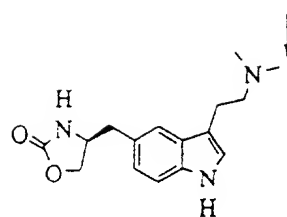


FIGURE 15

C3 SUBSTITUENT

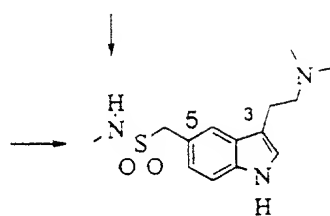


SUMATRIPTAN

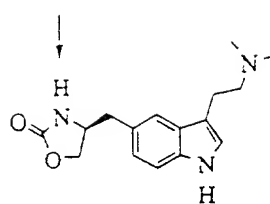


ZOLMITRIPTAN

C5 SUBSTITUENT



SUMATRIPTAN



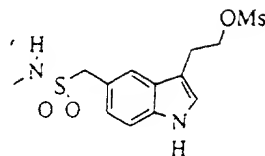
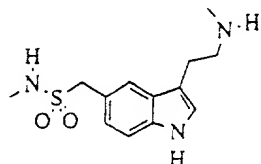
ZOLMITRIPTAN

FIGURE 16

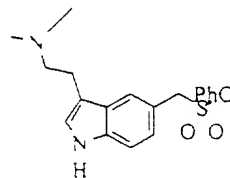
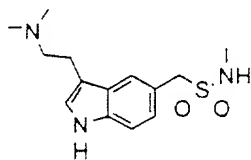


## SUMATRIPTAN BUILDING BLOCKS

### C3PharmacophoricBuilding Blocks



### C5PharmacophoricBuilding Blocks



### Pharmacophoric Building Blocks that contain a Spacer

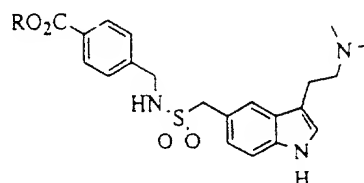
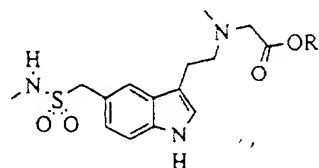
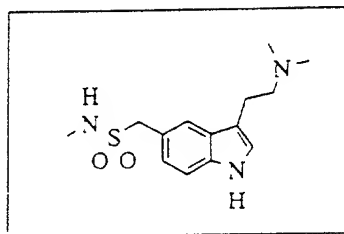
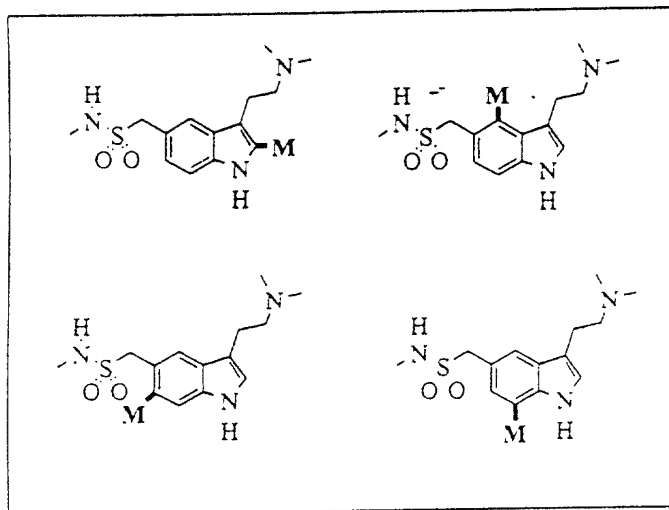


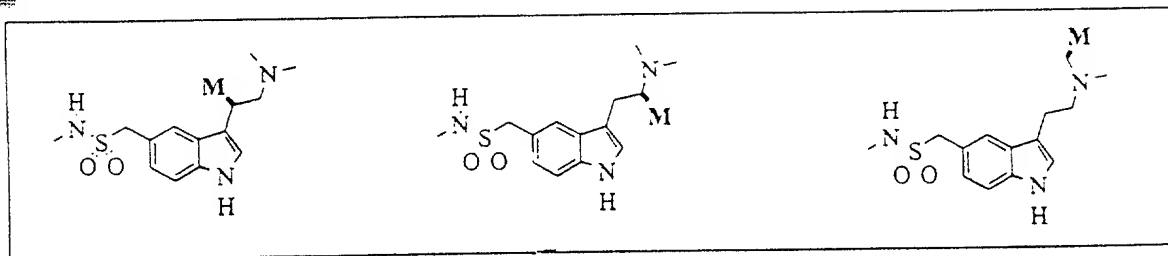
FIGURE 17

# MULTIVALOMERS OF SUMATRIPTAN

## 1. The Indole Core



## 2. C3 Substituent



## 3. C5 Substituent

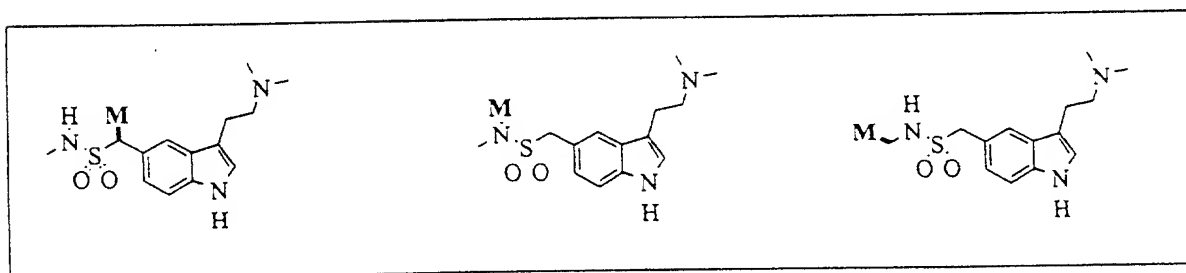
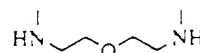
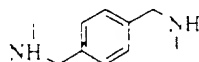
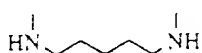
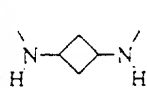
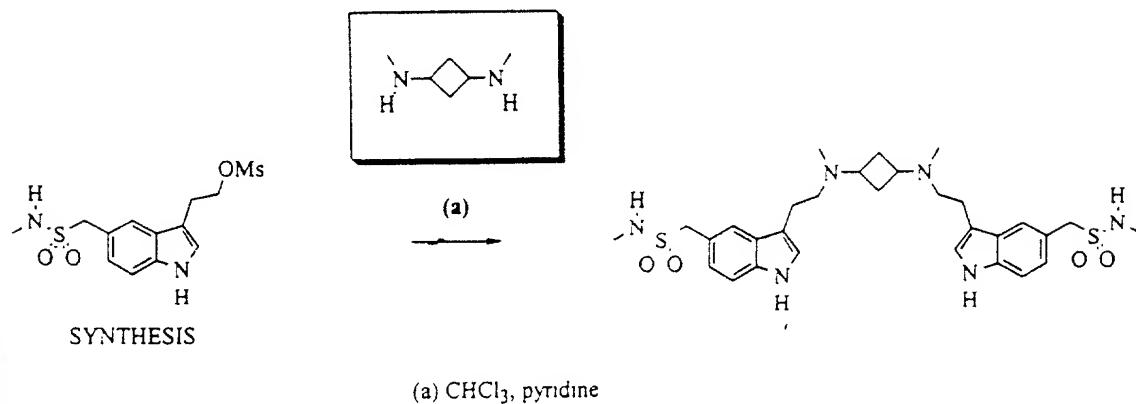
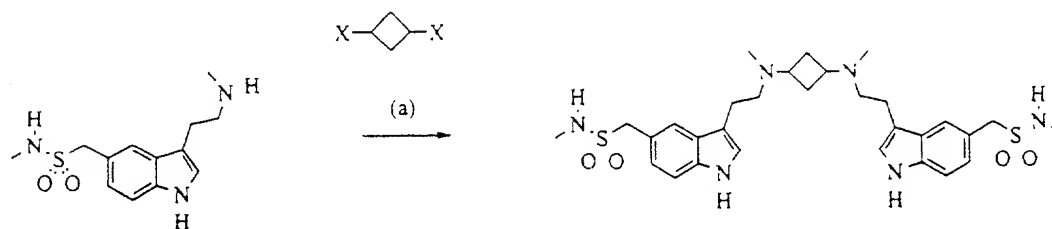


FIGURE 18

### C3 ELECTROPHILE TO PROVIDE MULTIVALOMERS

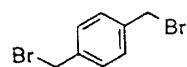


### C3 NUCLEOPHILE TO PROVIDE MULTIVALOMERS



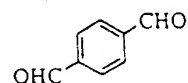
X =  $-\text{CH}_2\text{Br}$

(a) DCM, pyridine



X =  $-\text{CHO}$

(a) DCM,  $\text{NaBH}(\text{OAc})_3$ , AcOH



X =  $-\text{CO}_2\text{H}$

(a) DIC, DIPEA, DMF

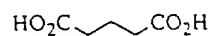
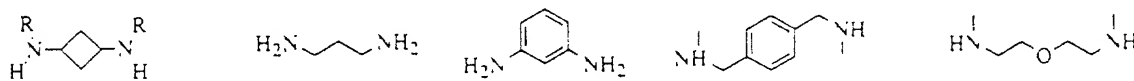
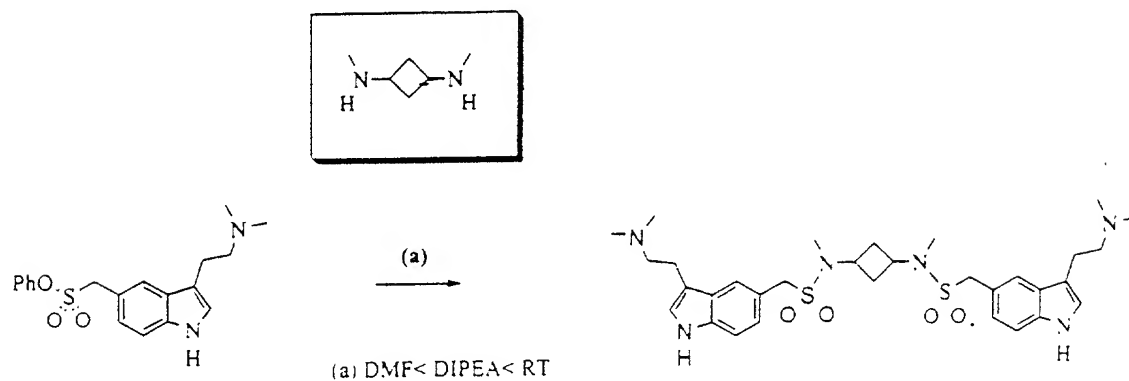


FIGURE 19

## C5 FUNCTIONALIZATION OF SUMATRIPTAN

### Electrophilic Pharmacophoric Monovalomer



### Nucleophilic Pharmacophoric Monovalomer

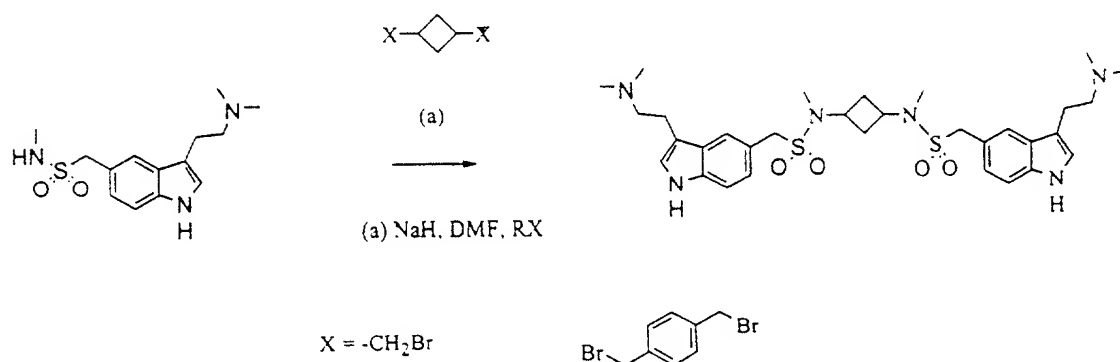
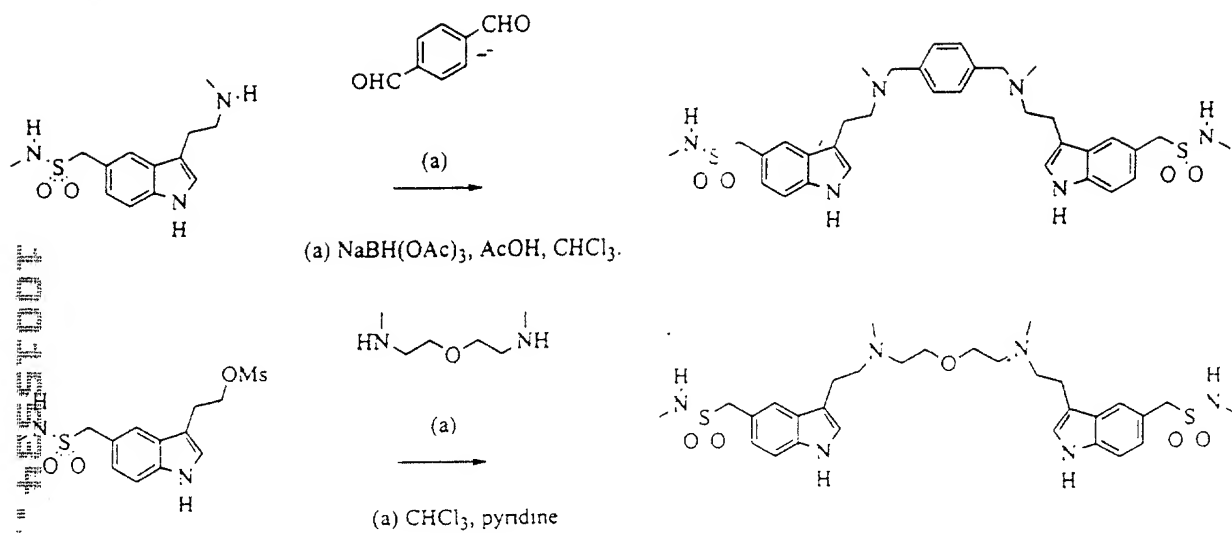


FIGURE 20

## SUMATRIPTAN SPECIFICS

### C3 Multivalomers



### C5 Multivalomers

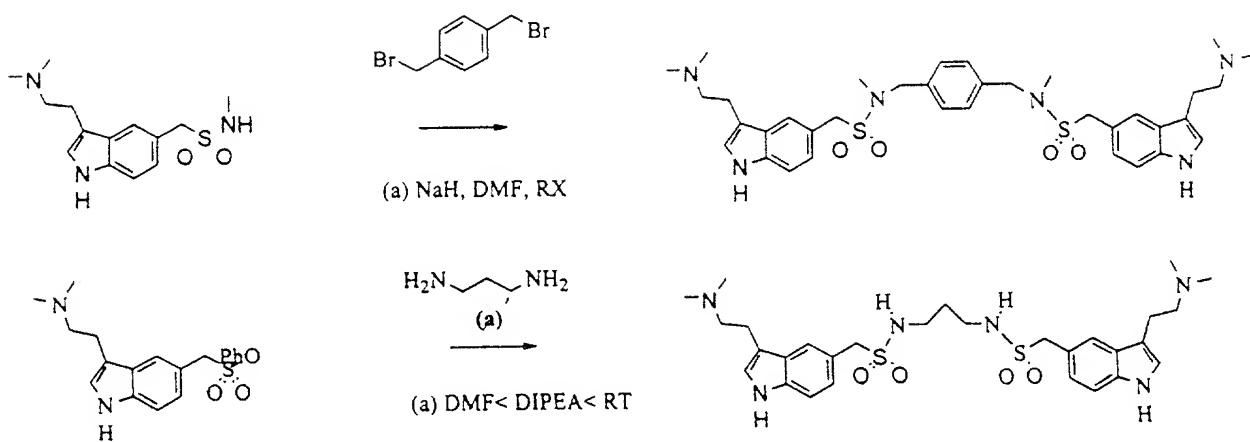
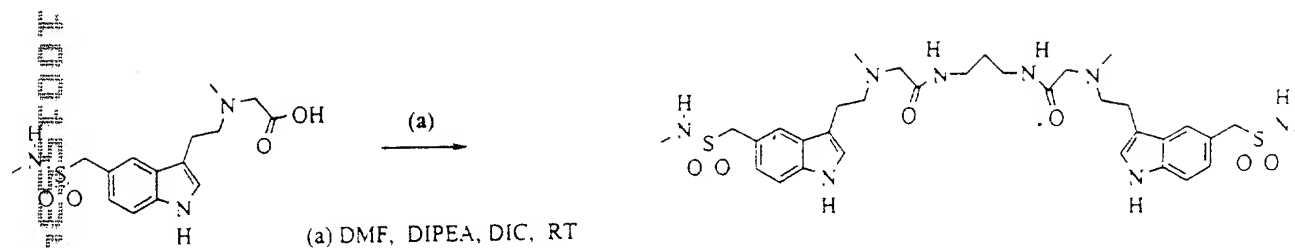
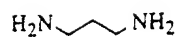


FIGURE 21

# SUMATRIPTAN SPACERS

## C3 Acid Spacer



## C5 Acid Spacer

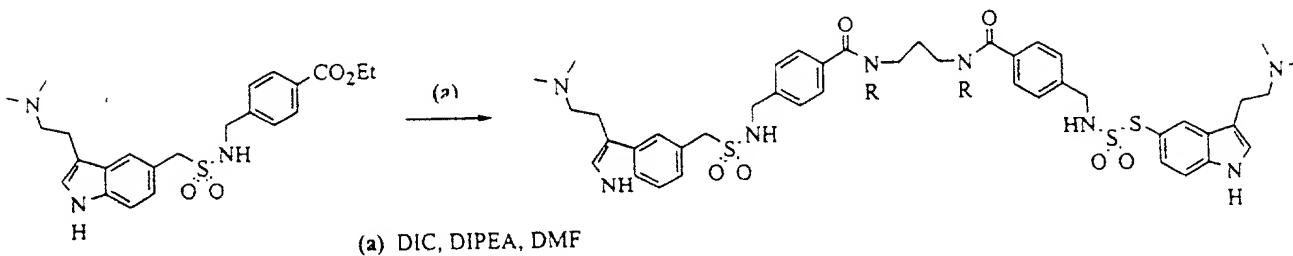
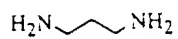
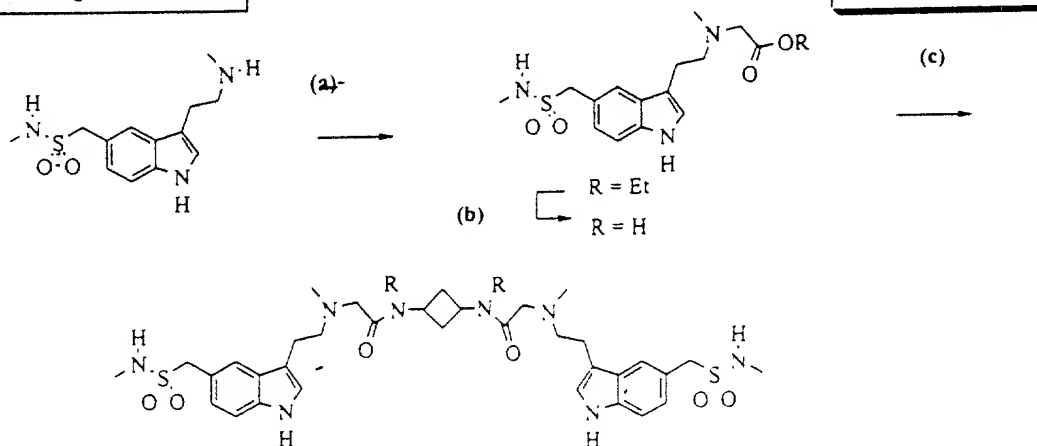


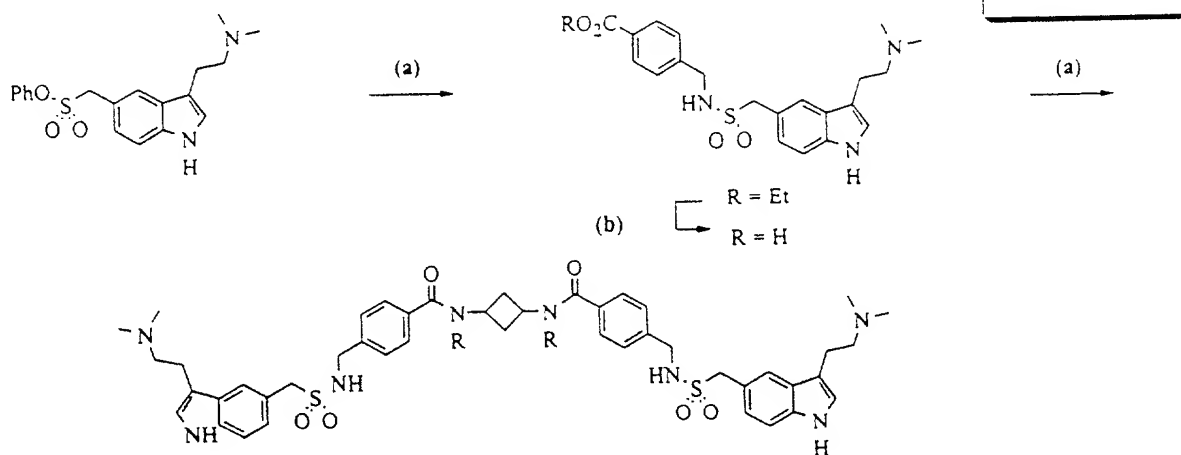
FIGURE 22

# Introduction of Spacer To Facilitate Multivalomer Formation

## C3 Sumatriptan Series



## C5 Sumatriptan Series



(a) DIPEA, DCM, BrCH2CO2Et (b) LiOH, THF, H2O. (c) DIC, DIPEA, DMF

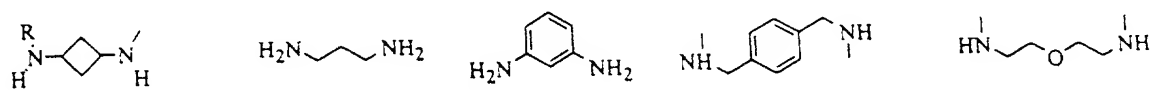
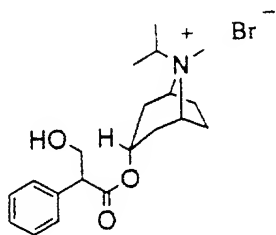
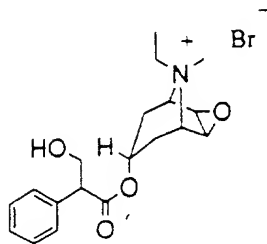


FIGURE 23

# MUSCARINIC ANTAGONISTS USED IN AIRWAY DISEASE

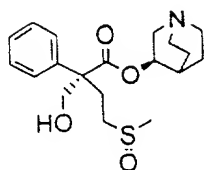


IPRATROPIUM BROMIDE

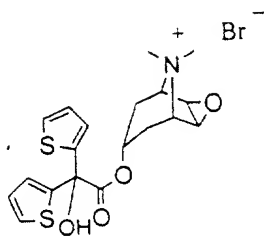


OXITROPIUM BROMIDE

i) Airway disease



REVATROPATE



TIOTROPIUM BROMIDE

FIGURE 24

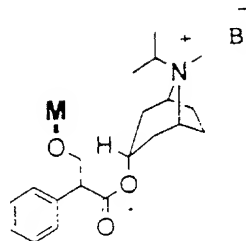
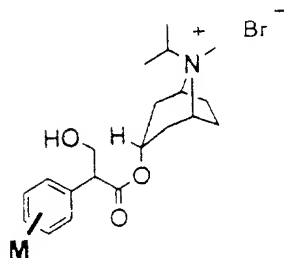
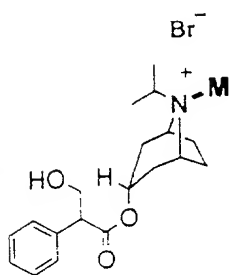


# SITES FOR DIMERIZATION

Nitrogen Atom of Tropane Core

Aromatic Ring

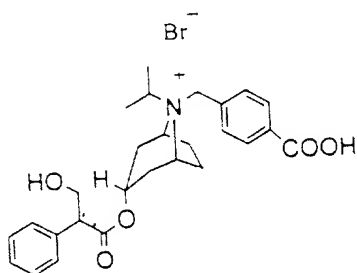
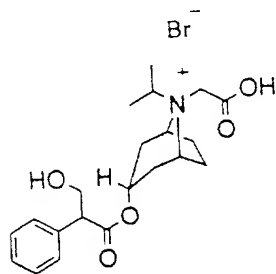
Primary Hydroxyl



## Suitable Pharmacophoric Building Blocks

Nitrogen Atom of Tropane Core

Acid Series



Amine Series

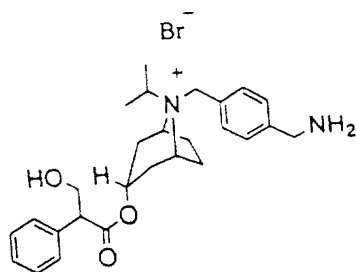
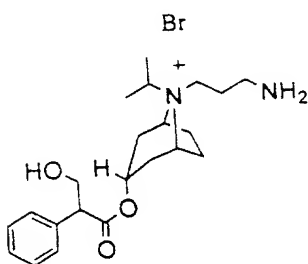
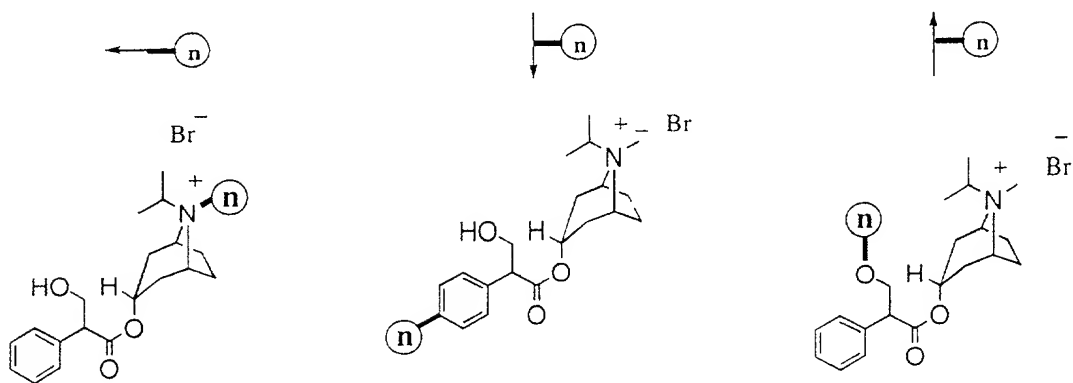


FIGURE 25

# Ipratropium Multivalomers 1-Different Points of Attachment



$n$  defines the valency of the multivalomer  
 $\bigcirc$  defines the framework core  
 $\longrightarrow$  distinguishes the differing points of attachment of ipratropium

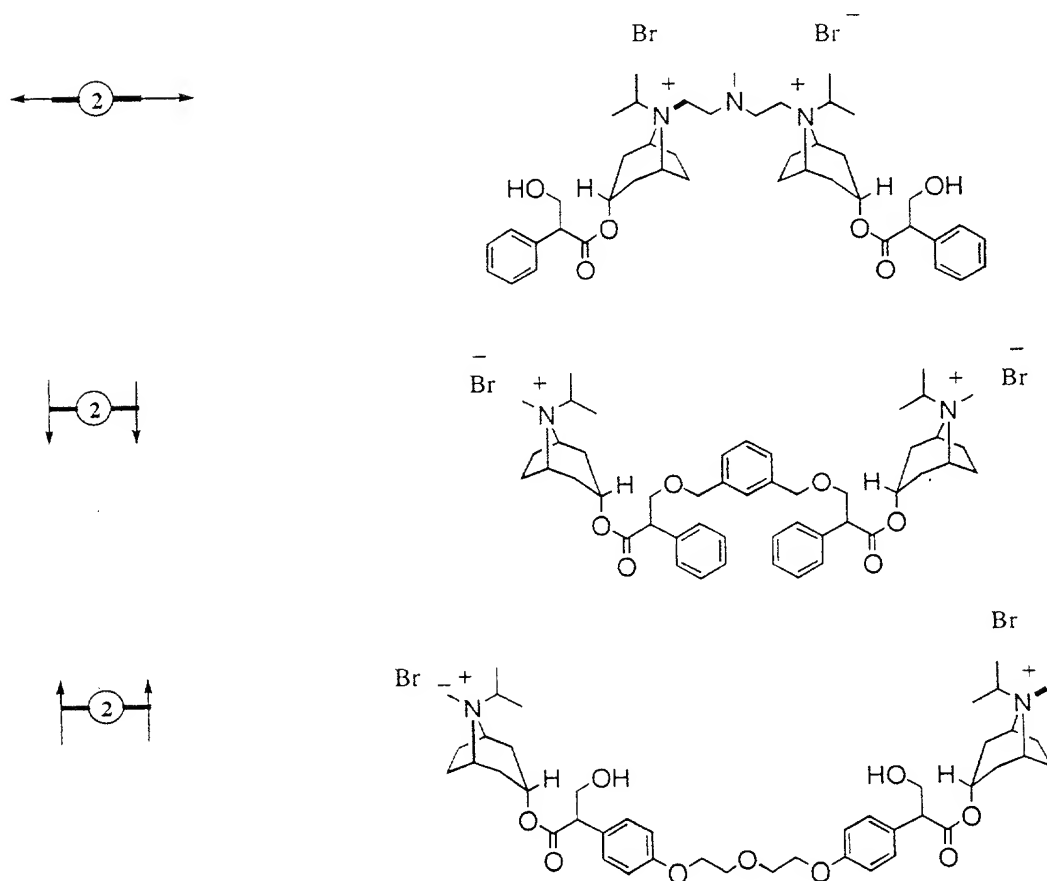
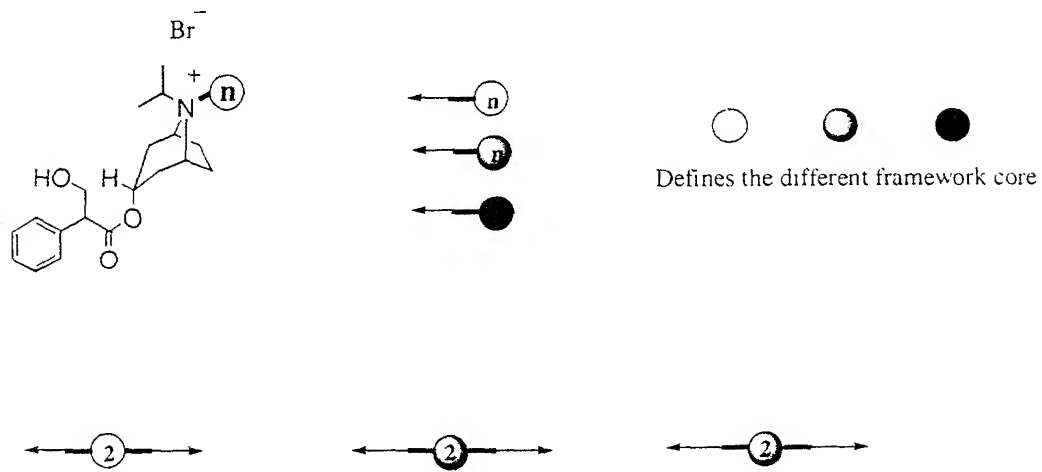


FIGURE 26

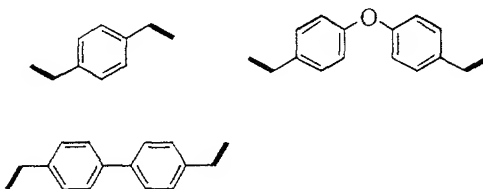
## Ipratropium Multivalomers 2-Alternative Framework Cores



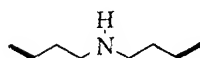
### 1. Alkyl Series



### 2. Aromatic Series



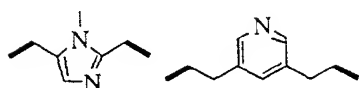
### 3. H-bond donor



### 4. H bond acceptor



### 5. Basic



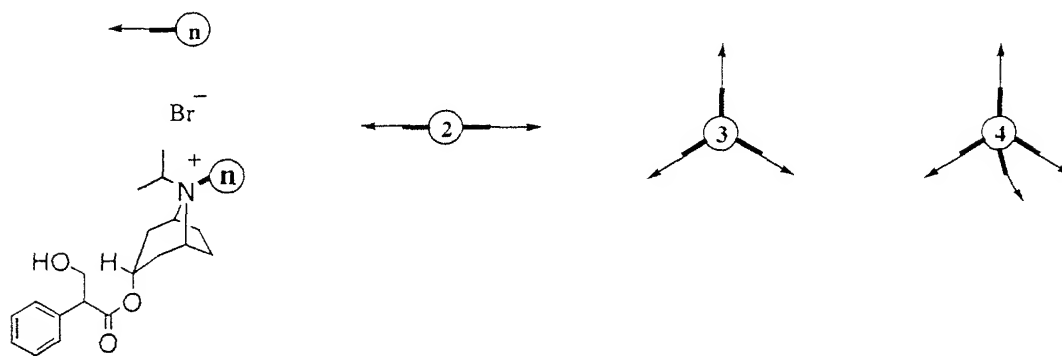
### 6. Acidic



FIGURE 27

# Ipratropium Multivalomers 3-Alternative Framework Valency

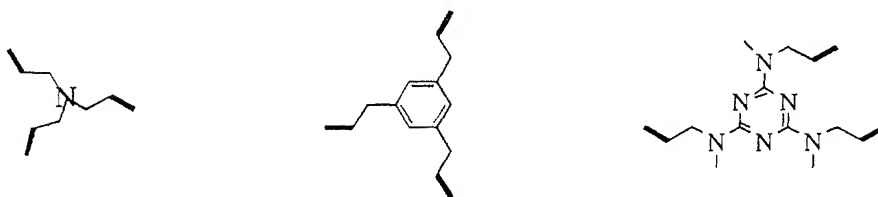
100534-12301



Dimeric Series



Trimeric Series



Tetrameric Series

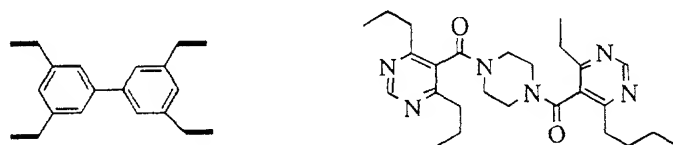


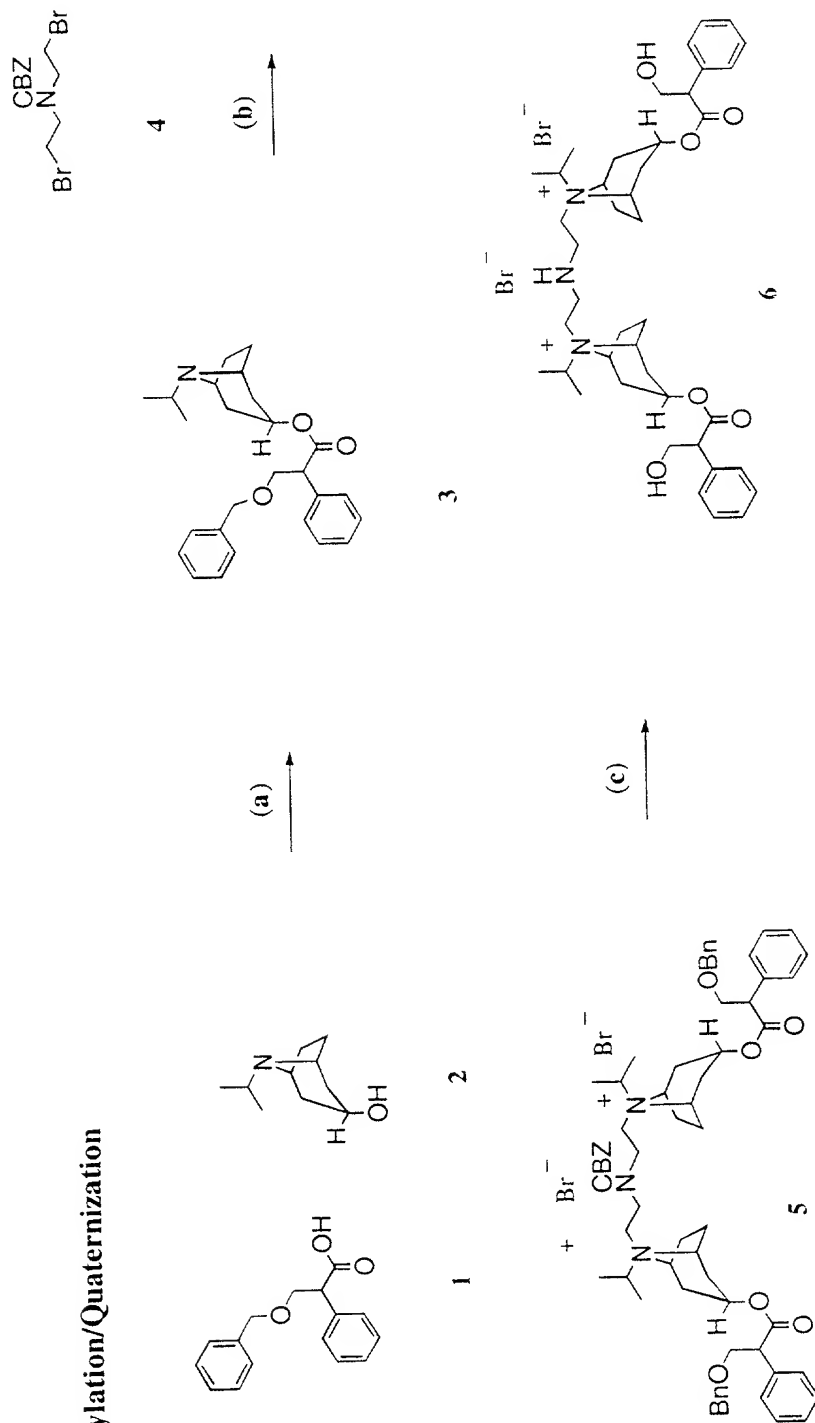
FIGURE 28

1221 1222 1223 1224 1225 1226 1227 1228 1229 1230 1231 1232 1233 1234 1235 1236 1237 1238 1239 1240 1241 1242 1243 1244 1245 1246 1247 1248 1249 1250 1251 1252 1253 1254 1255 1256 1257 1258 1259 1260 1261 1262 1263 1264 1265 1266 1267 1268 1269 1270 1271 1272 1273 1274 1275 1276 1277 1278 1279 1280 1281 1282 1283 1284 1285 1286 1287 1288 1289 1290 1291 1292 1293 1294 1295 1296 1297 1298 1299 1300 1301 1302 1303 1304 1305 1306 1307 1308 1309 1310 1311 1312 1313 1314 1315 1316 1317 1318 1319 1320 1321 1322 1323 1324 1325 1326 1327 1328 1329 1330 1331 1332 1333 1334 1335 1336 1337 1338 1339 1340 1341 1342 1343 1344 1345 1346 1347 1348 1349 1350 1351 1352 1353 1354 1355 1356 1357 1358 1359 1360 1361 1362 1363 1364 1365 1366 1367 1368 1369 1370 1371 1372 1373 1374 1375 1376 1377 1378 1379 1380 1381 1382 1383 1384 1385 1386 1387 1388 1389 1390 1391 1392 1393 1394 1395 1396 1397 1398 1399 1400 1401 1402 1403 1404 1405 1406 1407 1408 1409 1410 1411 1412 1413 1414 1415 1416 1417 1418 1419 1420 1421 1422 1423 1424 1425 1426 1427 1428 1429 1430 1431 1432 1433 1434 1435 1436 1437 1438 1439 1440 1441 1442 1443 1444 1445 1446 1447 1448 1449 1450 1451 1452 1453 1454 1455 1456 1457 1458 1459 1460 1461 1462 1463 1464 1465 1466 1467 1468 1469 1470 1471 1472 1473 1474 1475 1476 1477 1478 1479 1480 1481 1482 1483 1484 1485 1486 1487 1488 1489 1490 1491 1492 1493 1494 1495 1496 1497 1498 1499 1500 1501 1502 1503 1504 1505 1506 1507 1508 1509 1510 1511 1512 1513 1514 1515 1516 1517 1518 1519 1520 1521 1522 1523 1524 1525 1526 1527 1528 1529 1530 1531 1532 1533 1534 1535 1536 1537 1538 1539 1540 1541 1542 1543 1544 1545 1546 1547 1548 1549 1550 1551 1552 1553 1554 1555 1556 1557 1558 1559 1560 1561 1562 1563 1564 1565 1566 1567 1568 1569 1570 1571 1572 1573 1574 1575 1576 1577 1578 1579 1580 1581 1582 1583 1584 1585 1586 1587 1588 1589 1590 1591 1592 1593 1594 1595 1596 1597 1598 1599 1600 1601 1602 1603 1604 1605 1606 1607 1608 1609 1610 1611 1612 1613 1614 1615 1616 1617 1618 1619 1620 1621 1622 1623 1624 1625 1626 1627 1628 1629 1630 1631 1632 1633 1634 1635 1636 1637 1638 1639 1640 1641 1642 1643 1644 1645 1646 1647 1648 1649 1650 1651 1652 1653 1654 1655 1656 1657 1658 1659 1660 1661 1662 1663 1664 1665 1666 1667 1668 1669 1670 1671 1672 1673 1674 1675 1676 1677 1678 1679 1680 1681 1682 1683 1684 1685 1686 1687 1688 1689 1690 1691 1692 1693 1694 1695 1696 1697 1698 1699 1700 1701 1702 1703 1704 1705 1706 1707 1708 1709 1710 1711 1712 1713 1714 1715 1716 1717 1718 1719 1720 1721 1722 1723 1724 1725 1726 1727 1728 1729 1730 1731 1732 1733 1734 1735 1736 1737 1738 1739 1740 1741 1742 1743 1744 1745 1746 1747 1748 1749 1750 1751 1752 1753 1754 1755 1756 1757 1758 1759 1760 1761 1762 1763 1764 1765 1766 1767 1768 1769 1770 1771 1772 1773 1774 1775 1776 1777 1778 1779 1780 1781 1782 1783 1784 1785 1786 1787 1788 1789 1790 1791 1792 1793 1794 1795 1796 1797 1798 1799 1800 1801 1802 1803 1804 1805 1806 1807 1808 1809 1810 1811 1812 1813 1814 1815 1816 1817 1818 1819 1820 1821 1822 1823 1824 1825 1826 1827 1828 1829 1830 1831 1832 1833 1834 1835 1836 1837 1838 1839 1840 1841 1842 1843 1844 1845 1846 1847 1848 1849 1850 1851 1852 1853 1854 1855 1856 1857 1858 1859 1860 1861 1862 1863 1864 1865 1866 1867 1868 1869 1870 1871 1872 1873 1874 1875 1876 1877 1878 1879 1880 1881 1882 1883 1884 1885 1886 1887 1888 1889 1890 1891 1892 1893 1894 1895 1896 1897 1898 1899 1900 1901 1902 1903 1904 1905 1906 1907 1908 1909 1910 1911 1912 1913 1914 1915 1916 1917 1918 1919 1920 1921 1922 1923 1924 1925 1926 1927 1928 1929 1930 1931 1932 1933 1934 1935 1936 1937 1938 1939 1940 1941 1942 1943 1944 1945 1946 1947 1948 1949 1950 1951 1952 1953 1954 1955 1956 1957 1958 1959 1960 1961 1962 1963 1964 1965 1966 1967 1968 1969 1970 1971 1972 1973 1974 1975 1976 1977 1978 1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2



IPRATROPIUM 1-N-Linked Multivalomers

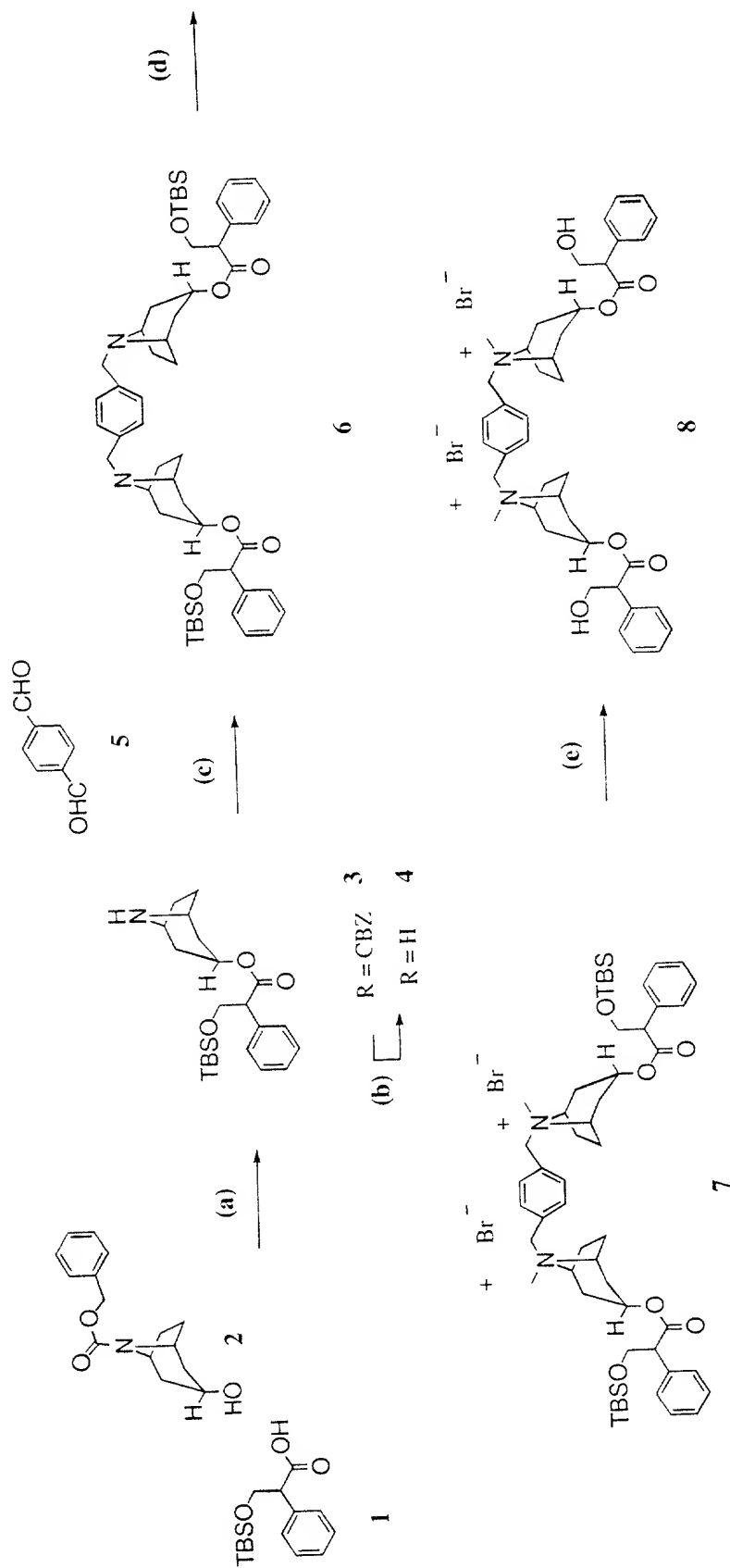
1. Alkylation/Quaternization



(a) DIC, DMAP, DMF (b)  $\text{CHCl}_3$  (c) Pd/C,  $\text{H}_2$ , EtOAc.

FIGURE 30

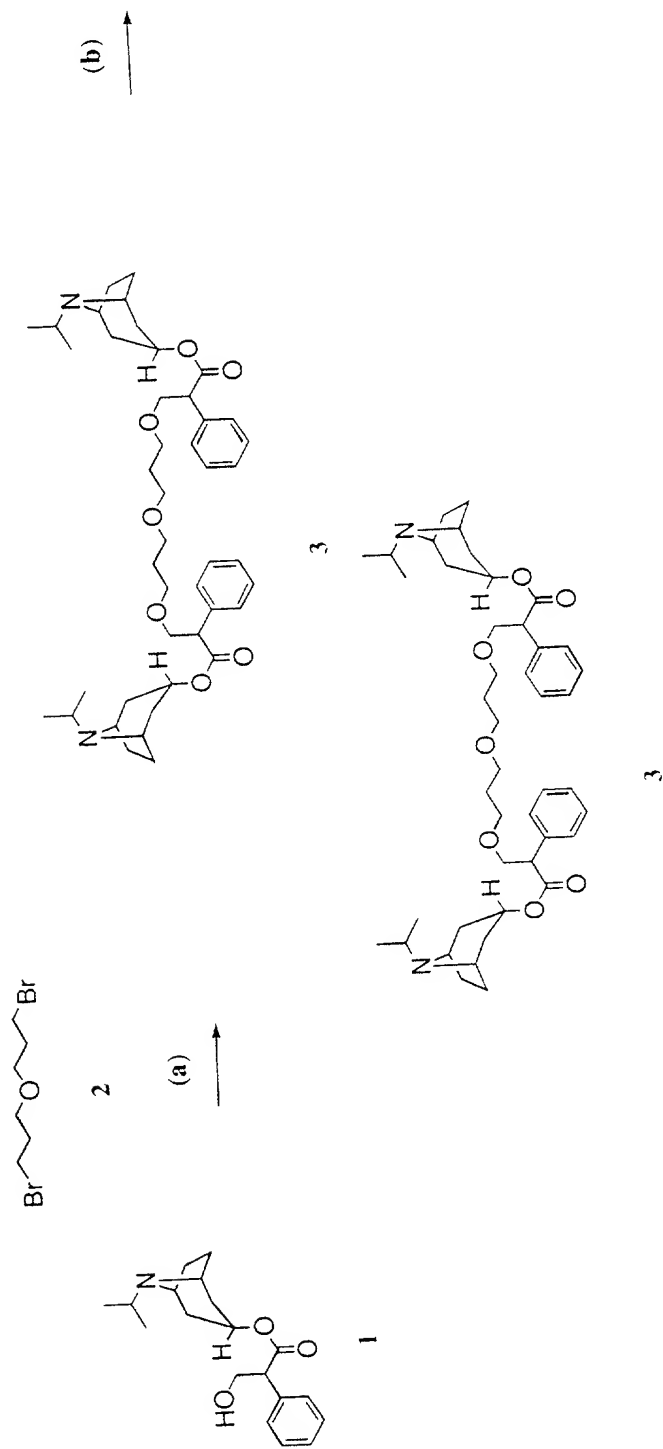
# 1. Reductive Amination/Quaternization



(a) DIC, DMF, DMF (b) Pd/C, H<sub>2</sub>, EtOAc (c) NaBH(OAc)<sub>3</sub>, CHCl<sub>3</sub>, AcOH (d) MeBr, CHCl<sub>3</sub> (e) TBAF, THF

FIGURE 31

IPRATROPIUM 3-O-Linked Multivalomers



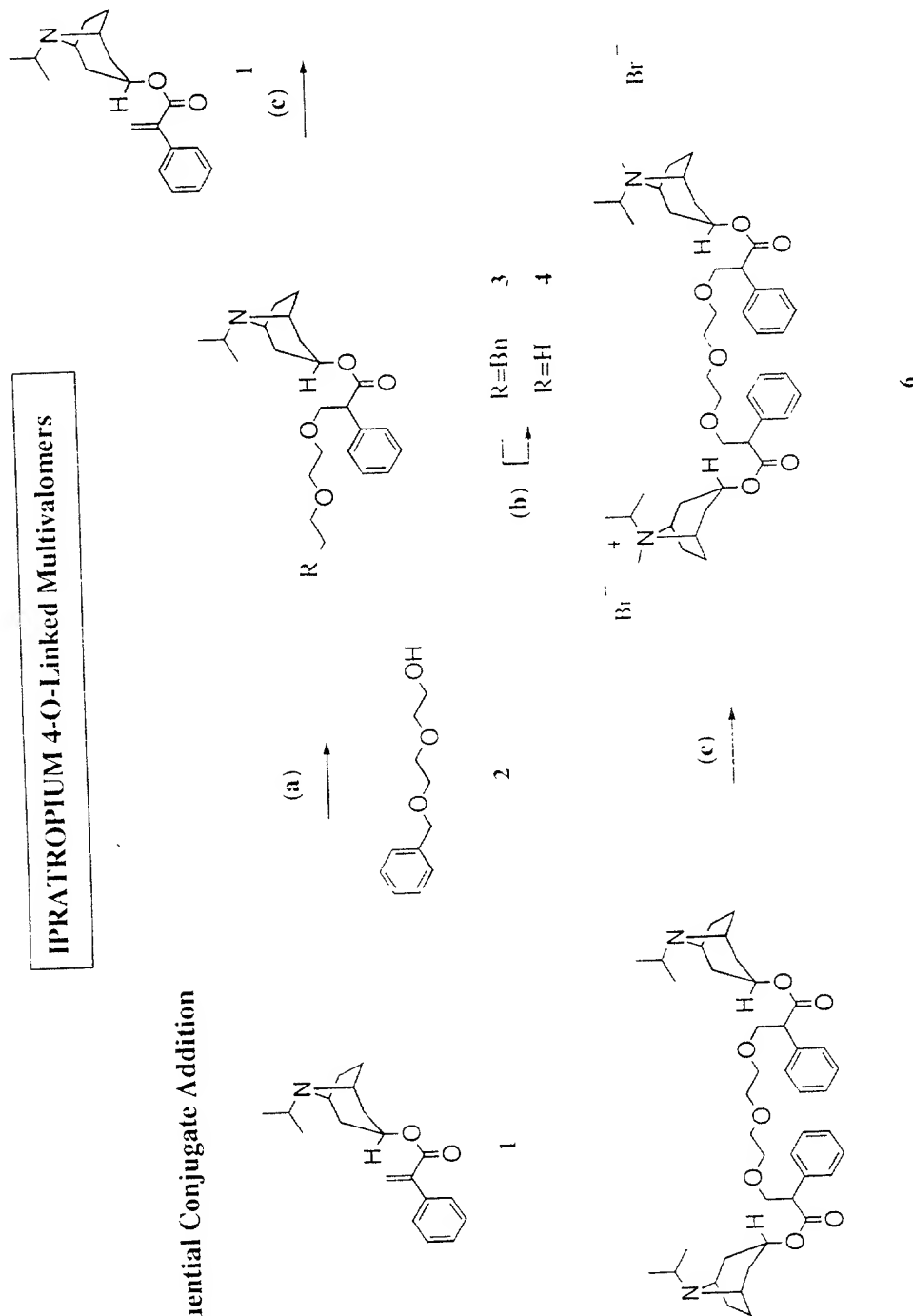
(a) NaH, THF (b) MeBr, CHCl<sub>3</sub>, reflux

FIGURE 32



IPRATROPIUM 4-O-Linked Multivalomers

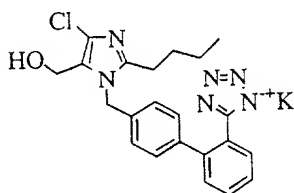
Sequential Conjugate Addition



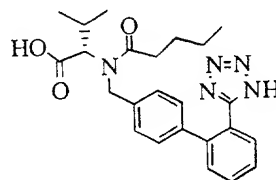
(a) NaH, DME, heat (b) Pd/C, H<sub>2</sub>, EtOAc (c) NaH, DME, heat (d) MeBr, CHCl<sub>3</sub>, heat

FIGURE 33

## AT1 RECEPTOR ANTAGONISTS

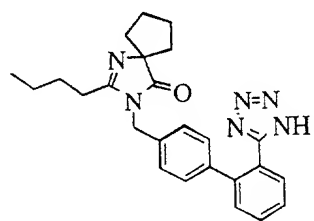


**LOSARTAN (Cozaar)**  
(Dupont Merck)

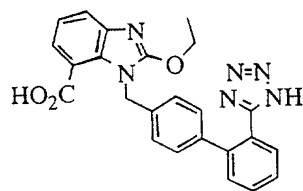


**VALSARTAN (Diovan)**  
(Novartis)

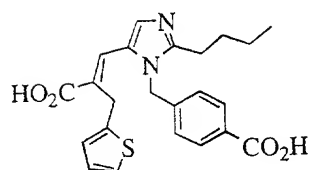
FIGURE 34



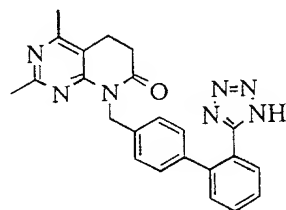
**IRBESARTAN**  
(Sanofi)



**CANDESARTAN (Atacand)**  
(Takeda)

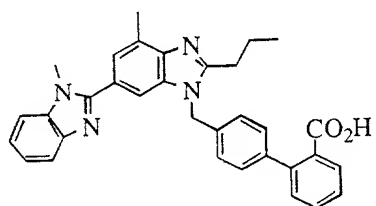


**EPROSARTAN (Tevetan)**  
(Smith KlineBeecham)



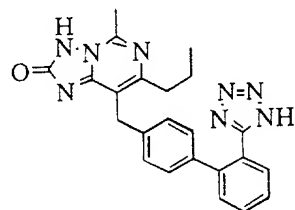
**TASOSARTAN (Verdia)**  
(Wyeth-Ayerst)

**FIGURE 35**



**TELMISARTAN**  
(Boehringer Ingelheim)

Phase III



**RIPISARTAN**  
(Bristol Myers Squibb)

Phase II

## Phase II

CS-866 Sankyo

DA-727 Daiichi

KRH-594 Wakunga

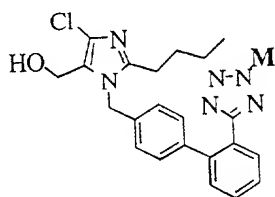
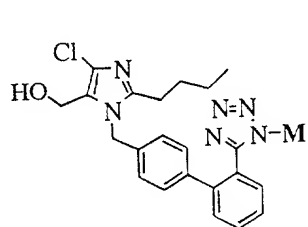
LR-B/081 Lusofarmaco

TAK-536 Takeda

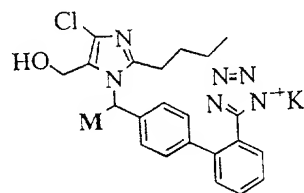
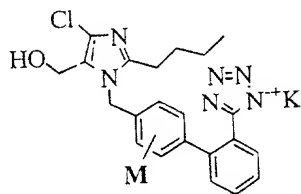
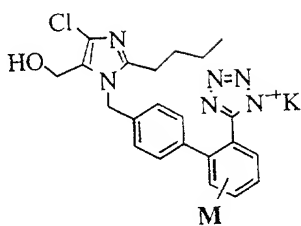
YM-358 Yamanouchi

FIGURE 36

# 1. Tetrazole



## Biaryl Motif



## 3. Imidazole Substituents

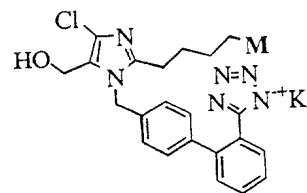
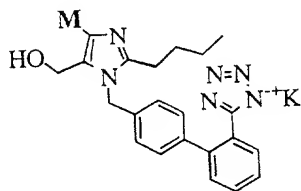
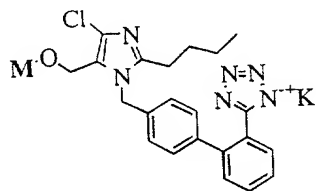
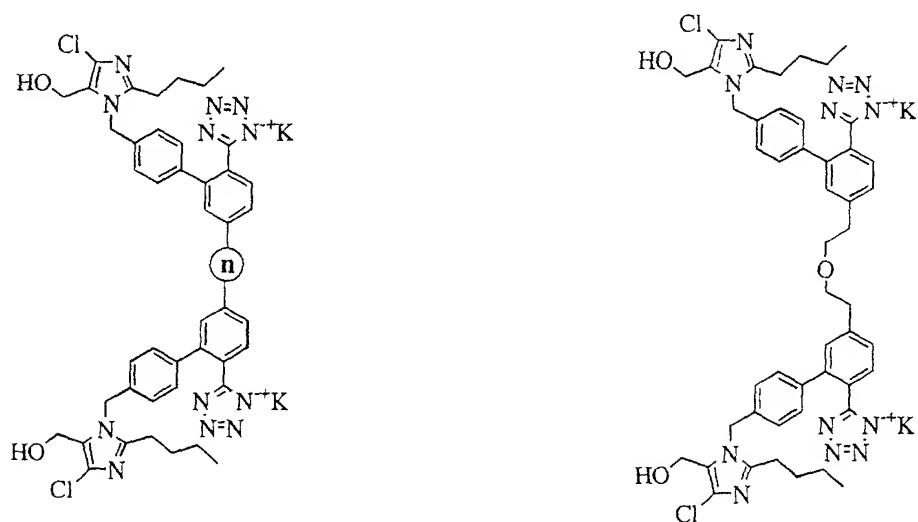


FIGURE 37

## Losartan Multivalomers 1-Differing Points of Attachment

### 1. Aryl Linked Multivalomers



### 2. Butyl Linked Multivalomers

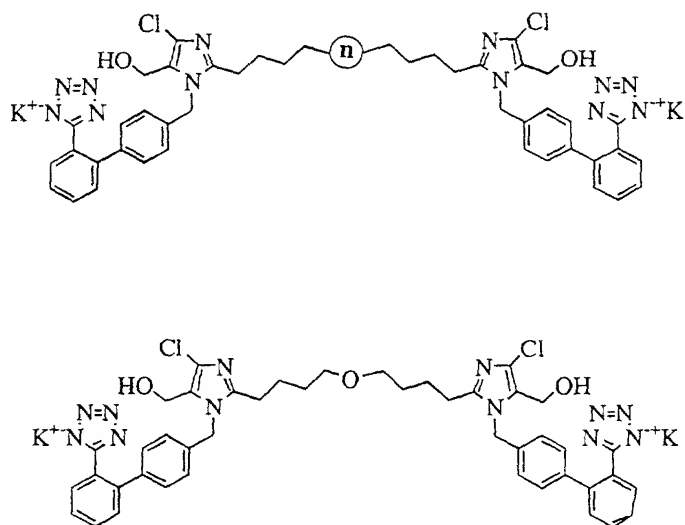
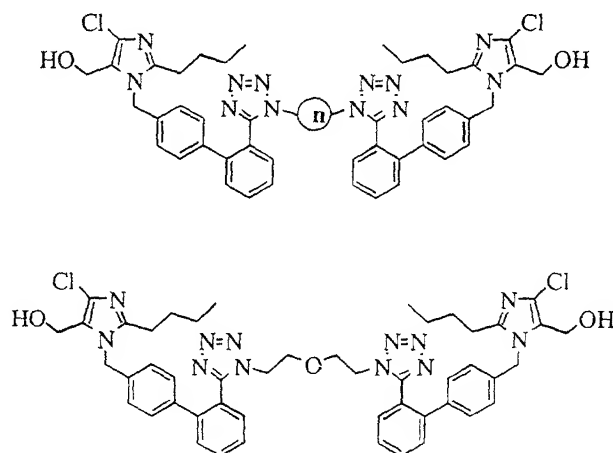


FIGURE 38

# Losartan Multivalomers 1-Differing Points of Attachment

## 1. Tetrazole Linked Multivalomers



## 2. Aryl Linked Multivalomers

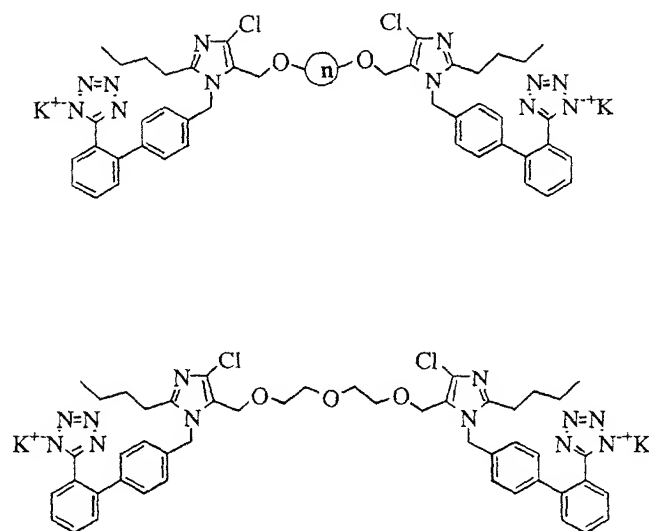
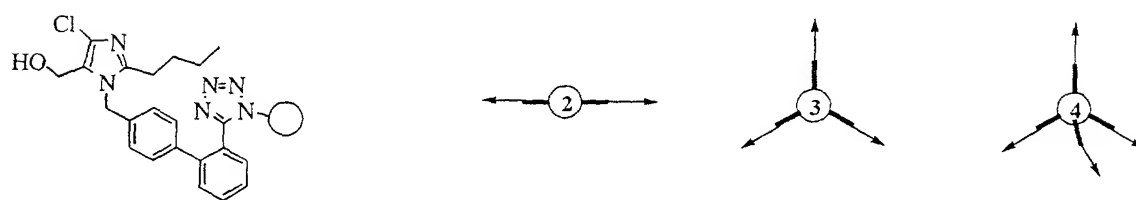
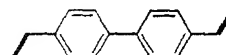
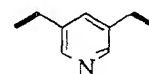
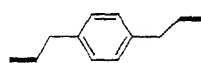
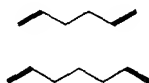
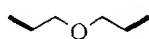


FIGURE 39

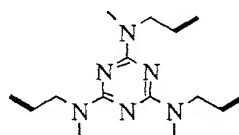
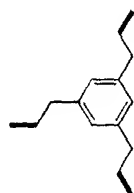
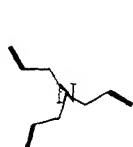
# Lorsartan Multivalomers 2-Differing Valency of Multivalomer



## Dimeric Series



## Trimeric Series



## Tetrameric Series

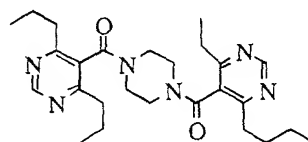
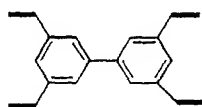
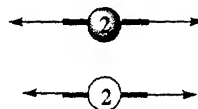
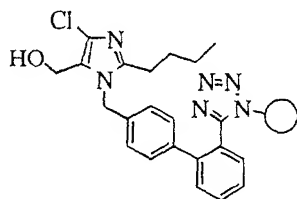


FIGURE 40



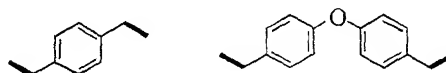
# Lorsartan Multivalomers 3-Differing Framework Building Blocks



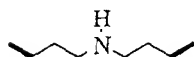
## 1. Alkyl Series



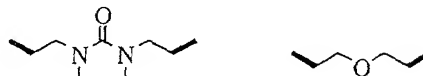
## 2. Aromatic Series



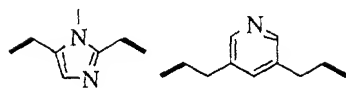
## 3. H-bond donor



## 4. H bond acceptor



## 5. Basic

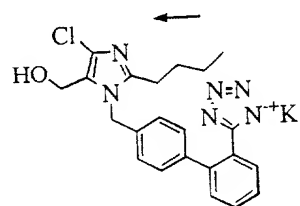


## 6. Acidic



FIGURE 41

# Losartan Multivalomers 4-Different Relative Connectivity



LOSARTAN (Cozaar)

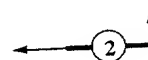
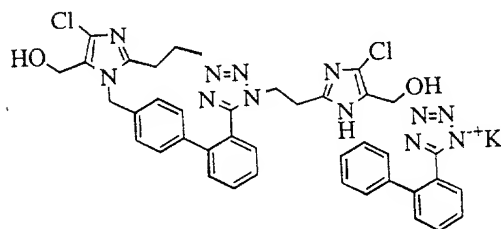
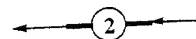
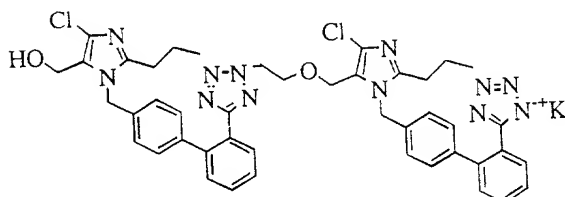
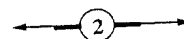
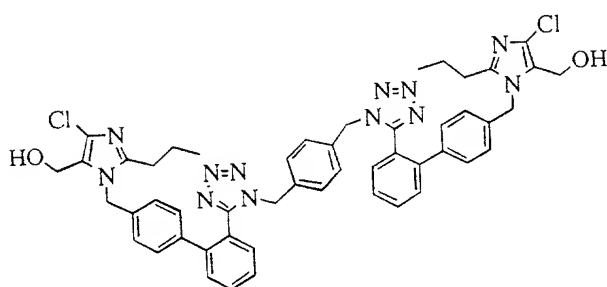
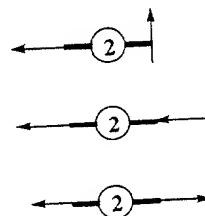
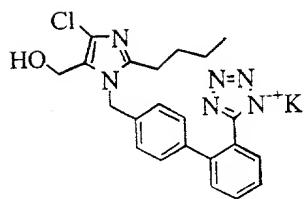
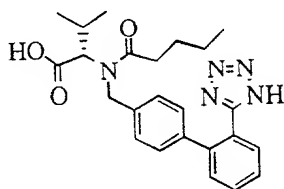


FIGURE 42

# Losartan Multivalomers 5-Heterovalomers

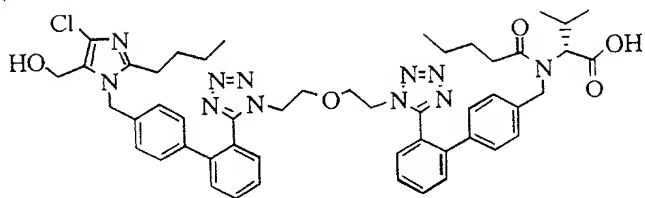
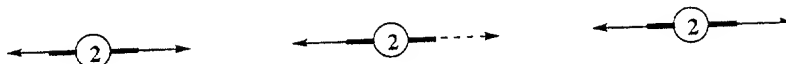


LOSARTAN (Cozaar)



VALSARTAN (Diovan)

Heterovalomers



Losartan/Valsartan



FIGURE 43

Losartan Multivalomer Synthesis 1-Hydroxyl Linked Multivalomer

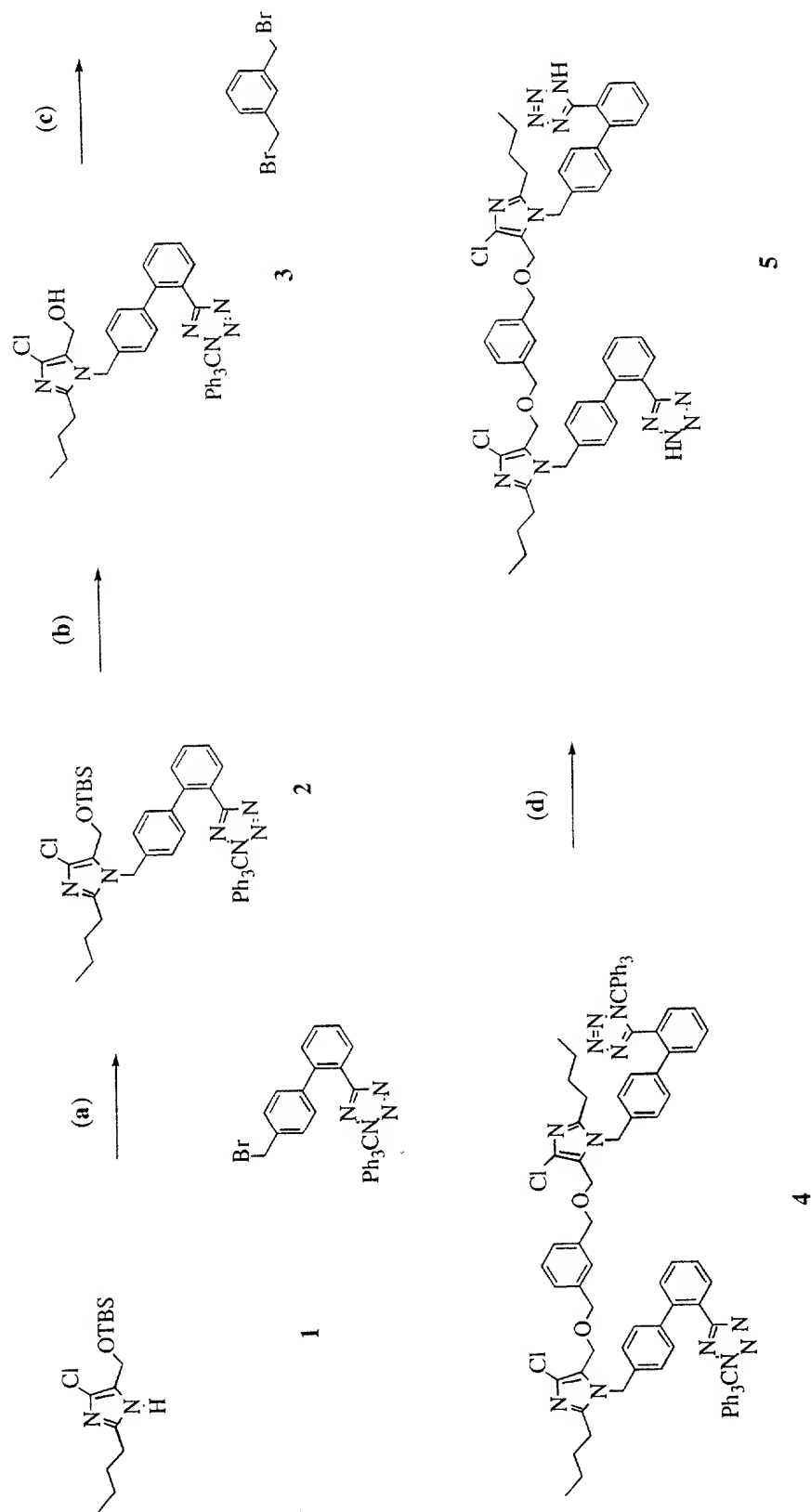
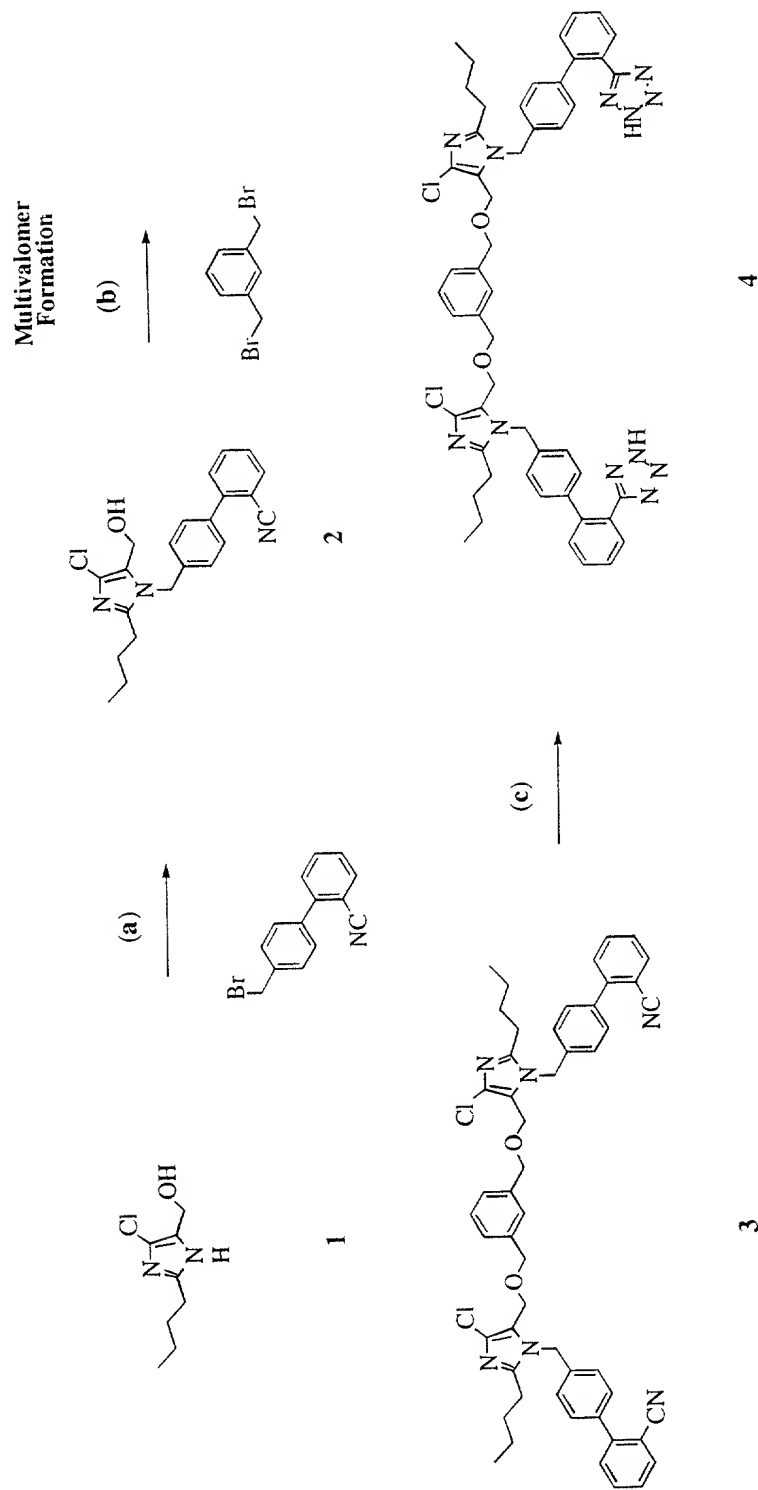


FIGURE 44

Losartan Multivalomer Synthesis 2-Hydroxyl Linked Multivalomer

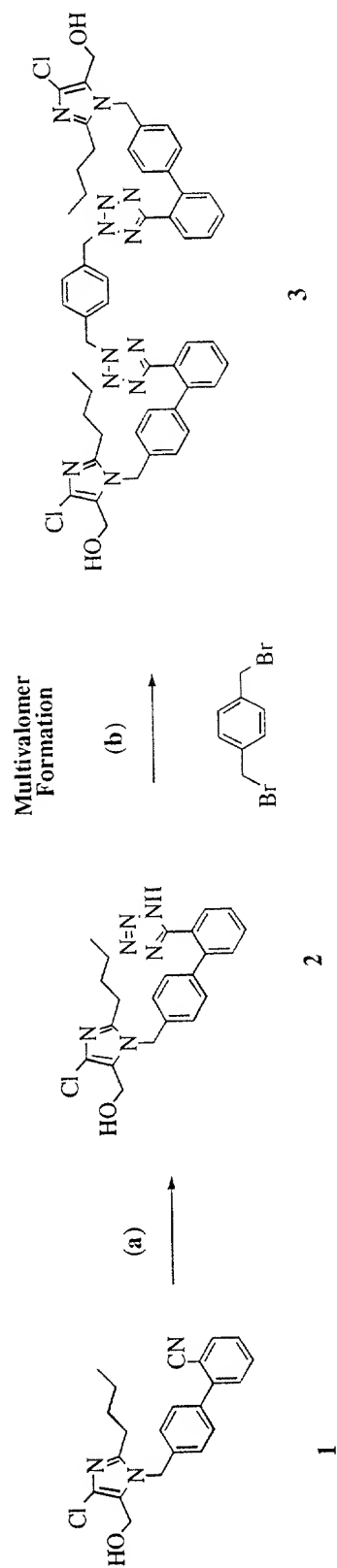


(a) NaOMe, MeOH, DMF (b) NaH, DMF (c)  $\text{Bu}_3\text{SnN}_3$ , xylene, reflux

FIGURE 45

Losartan Multivalomer Synthesis 3-Tetrazole Linked Multivalomers

Strategy-Selective tetrazole alkylation in the presence of the primary hydroxyl



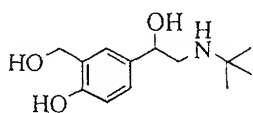
(a)  $\text{Bu}_3\text{SnN}_3$ , xylene, 24hr reflux (b)  $\text{NaOH}$ , THF

For precedent see Carini, D. J., *J. Med. Chem.*, 1991, 34, 2525-2547

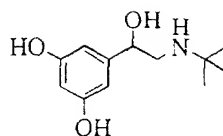
FIGURE 46

## β<sub>2</sub> Adrenergic Drugs

### 1. Rapid Onset Inhaled Drugs

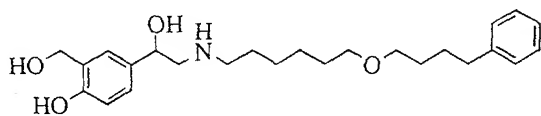


**Albuterol**  
(GlaxoWellcome)

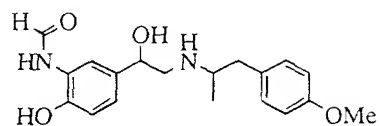


**Terbutaline**

### 2. Prolonged Duration of Action Inhaled Drugs



**Salmeterol**  
(GlaxoWellcome)



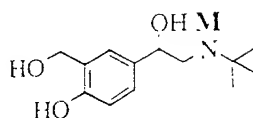
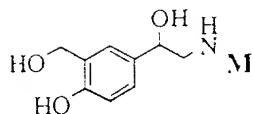
**Formoterol**  
(Novartis)

**Notes-** 1. These drugs are racemates. Multivalomers will produce diastereomers.

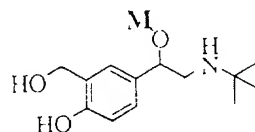
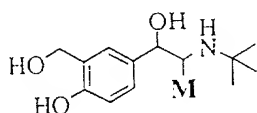
**FIGURE 47**

# Albuterol Multivalomers

## 1. N atom

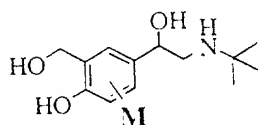


## 2. Ethanolamine function

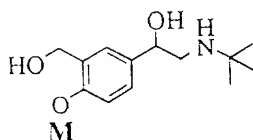


## 3. Phenyl Ring

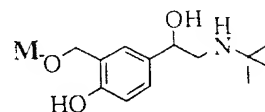
### New Substitution



### Phenolic Group



### Benzyl Alcohol

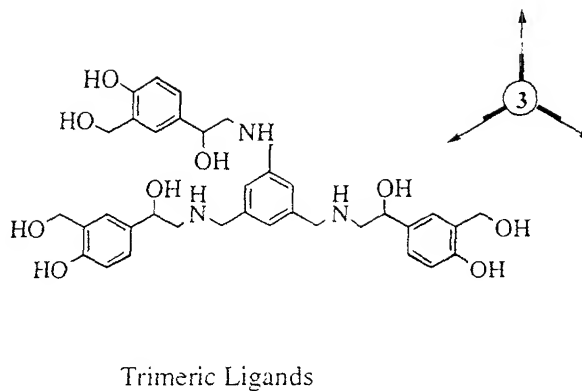
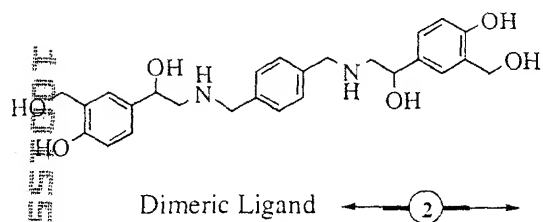


M represents a site for the attachment of the monovalomer to the framework core

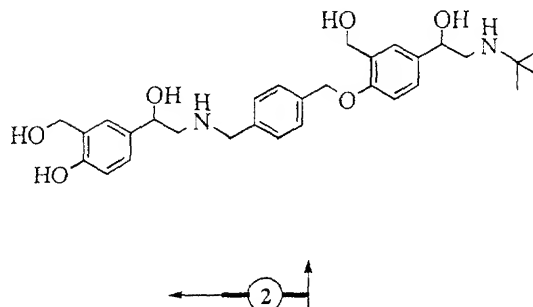
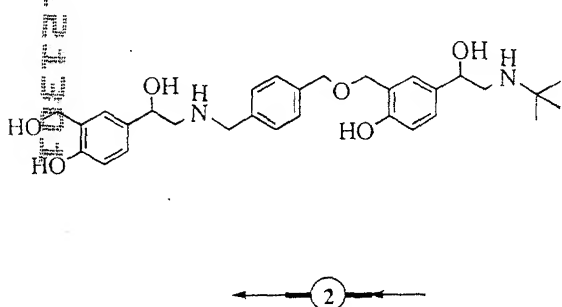
FIGURE 48



### 1. Valency of Framework Building Block



### 2. Relative Orientation of Monovalomer Building Blocks.



### 3. Mixed Multivalomers Derived from Different $\beta_2$ -agonists

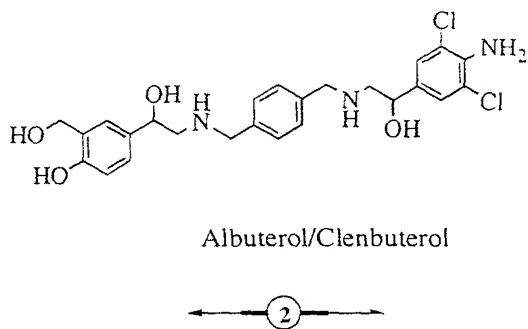
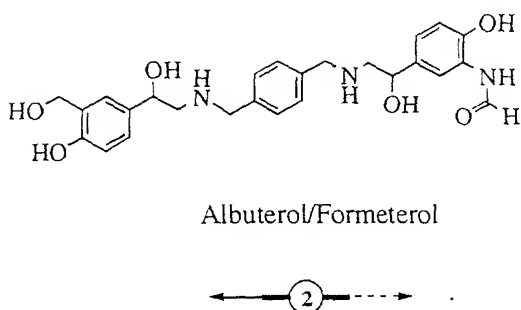
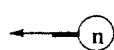


FIGURE 49

# Albuterol Multivalomers 1-Different Points of Attachment



**n**

defines the valency of the multivalomer



defines the framework core

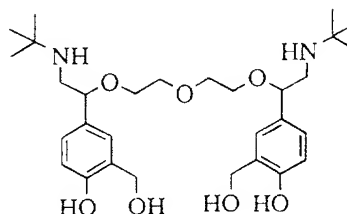
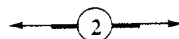
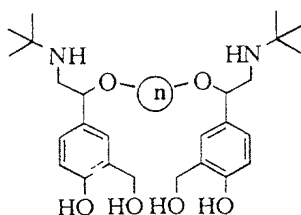


distinguishes the different points of attachment of albuterol

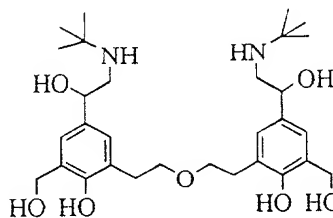
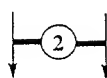
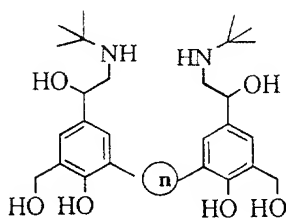
## Generic Examples

## Specific Example

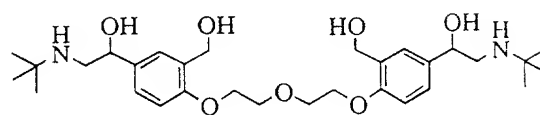
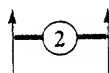
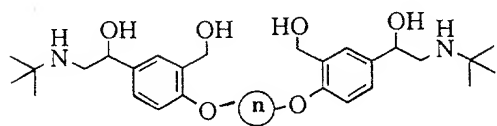
### Series 1



### Series 2



### Series 3



### Series 4

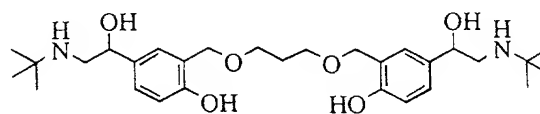
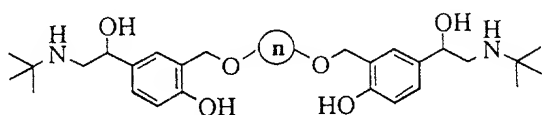
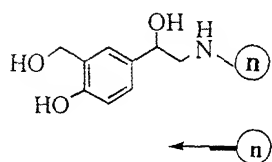


FIGURE 50

# Albuterol Multivalomers 2-Alternative Framework Cores

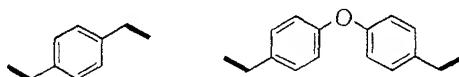


Albuterol Multivalomers 2-Alternative Framework Cores

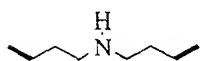
## 1. Alkyl Series



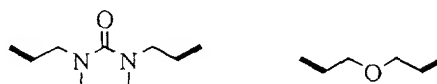
## 2. Aromatic Series



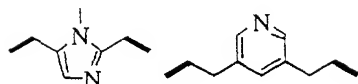
## 3. H-bond donor



## 4. H bond acceptor



## 5. Basic

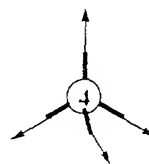
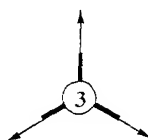
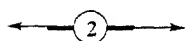
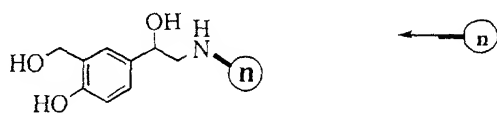


## 6. Acidic

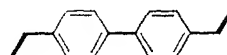
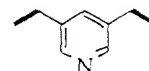
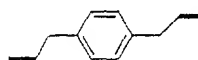
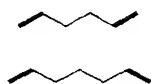
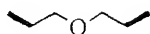


FIGURE 51

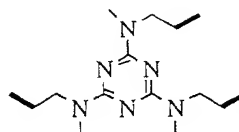
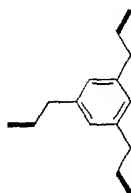
# Albuterol Multivalomers 3-Alternative Framework Valency



## Dimeric Series



## Trimeric Series



## Tetrameric Series

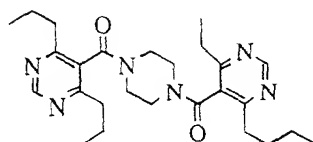
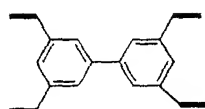
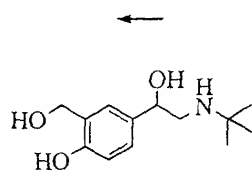


FIGURE 52

# Albuterol Multivalomers 4-Relative Pharmacophore Orientation

## Pharmacophore Orientation



Albuterol

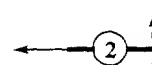
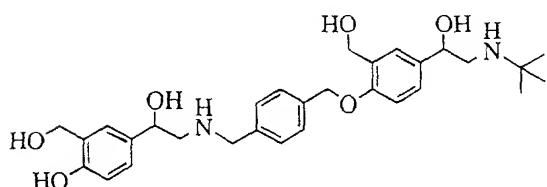
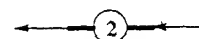
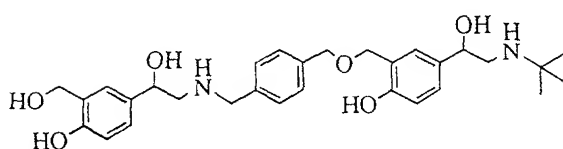
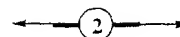
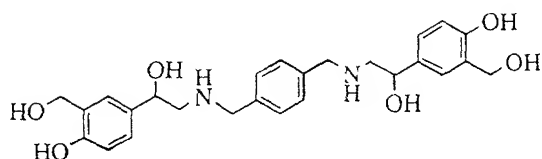
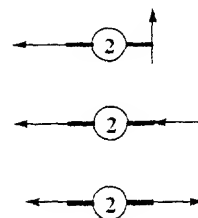
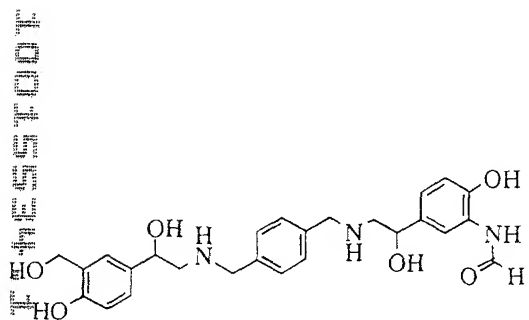
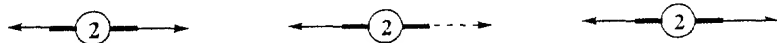


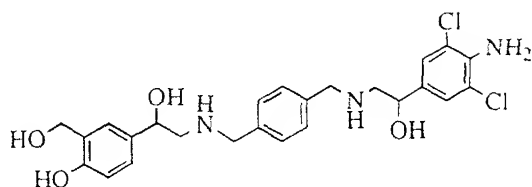
FIGURE 53

Albuterol Multivalomers 5-Mixed  $\beta_2$  Adrenergic Heterovalomers

## Heterovalomers



Albuterol/Formeterol



Albuterol/Clenbuterol

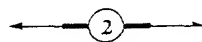
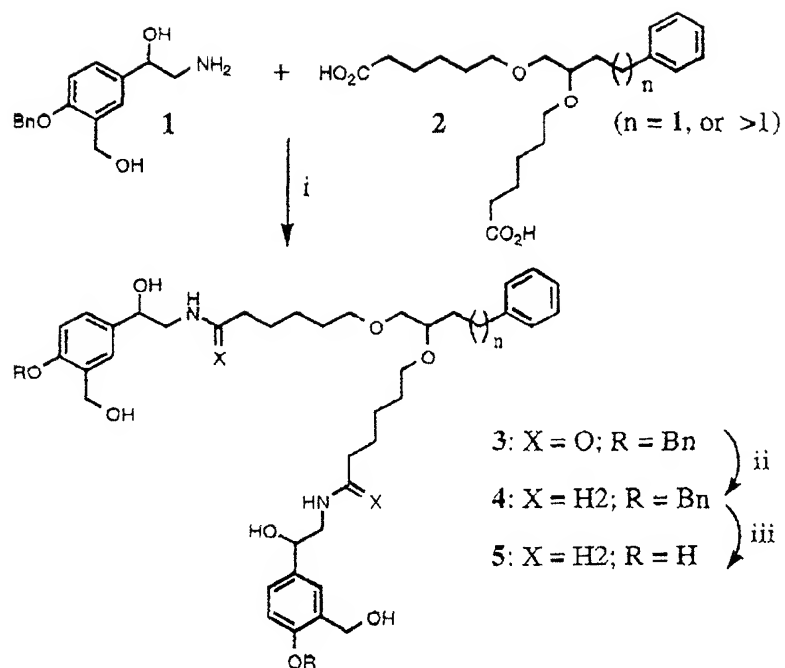
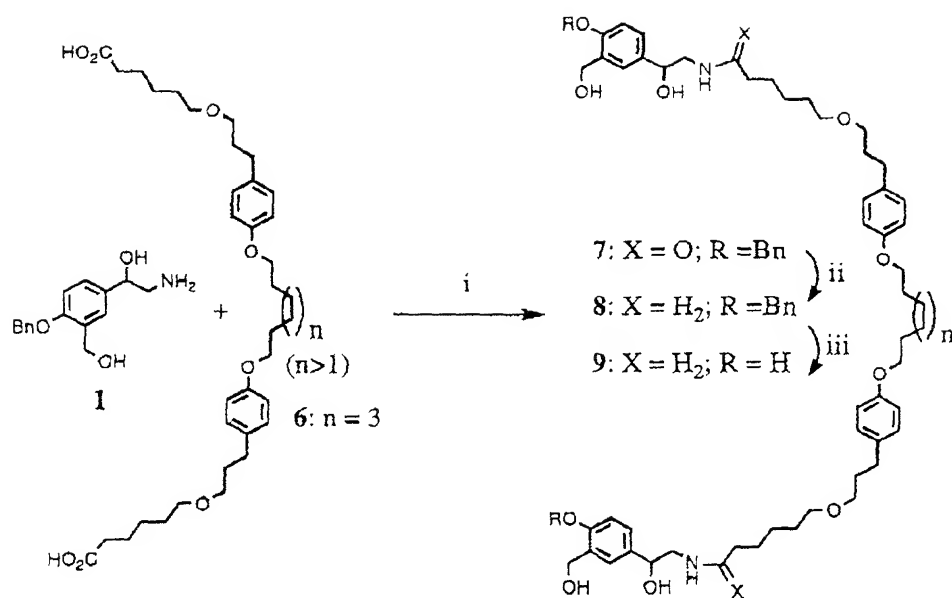


FIGURE 54



reagents and conditions: i) HOBt, PyBOP, DIPEA, DMF, rt, 24 h;  
 ii) LiAlH<sub>4</sub>, THF, 0°C to 80°C; iii) H<sub>2</sub> (1 atm), 10% Pd/C, EtOH, rt, 24 h

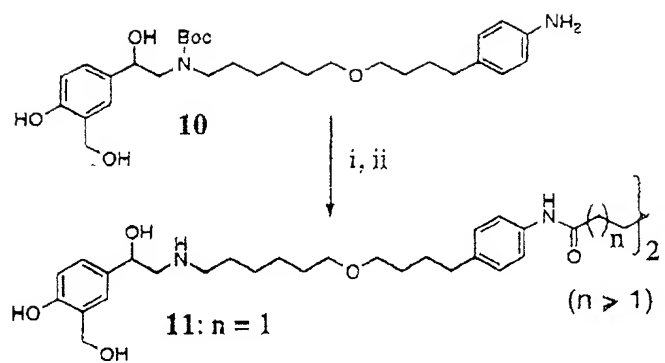
FIGURE 55



reagents and conditions: i) HOBt, PyBOP, DIPEA, DMF, rt, 24 h;  
 ii)  $LiAlH_4$ , THF,  $0^\circ C$  to  $80^\circ C$ ; iii)  $H_2$  (1 atm), 10% Pd/C, EtOH, rt, 24 h

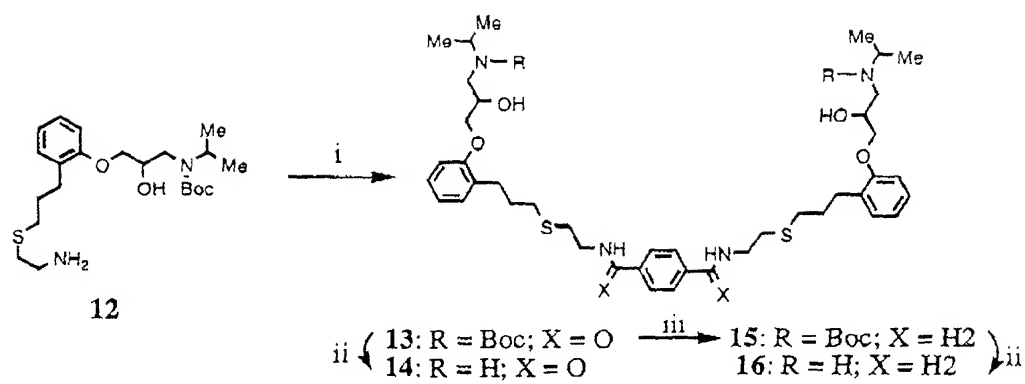
FIGURE 56





reagents and conditions: i) 1,6-hexanedioic acid, DIPEA, HOBT, PyBOP, DMF, rt;  
 ii) TFA/CH<sub>2</sub>Cl<sub>2</sub>, 0°C

FIGURE 57



reagents and conditions: i) terphthalic acid, DIPEA, HOBT, PyBOP, DMF, rt;  
 ii) TFA/CH<sub>2</sub>Cl<sub>2</sub>, 0°C; iii) LiAlH<sub>4</sub>, THF, 80°C

FIGURE 58